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Approved Antiviral Drugs over the Past 50 Years

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SUMMARY

Since the first antiviral drug, idoxuridine, was approved in 1963, 90 antiviral drugs categorized into 13 functional groups have been formally approved for the treatment of the following 9 human infectious diseases: (i) HIV infections (protease inhibitors, integrase inhibitors, entry inhibitors, nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and acyclic nucleoside phosphonate analogues), (ii) hepatitis B virus (HBV) infections (lamivudine, interferons, nucleoside analogues, and acyclic nucleoside phosphonate analogues), (iii) hepatitis C virus (HCV) infections (ribavirin, interferons, NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors), (iv) herpesvirus infections (5-substituted 2′-deoxyuridine analogues, entry inhibitors, nucleoside analogues, pyrophosphate analogues, and acyclic guanosine analogues), (v) influenza virus infections (ribavirin, matrix 2 protein inhibitors, RNA polymerase inhibitors, and neuraminidase inhibitors), (vi) human cytomegalovirus infections (acyclic guanosine analogues, acyclic nucleoside phosphonate analogues, pyrophosphate analogues, and oligonucleotides), (vii) varicella-zoster virus infections (acyclic guanosine analogues, nucleoside analogues, 5-substituted 2′-deoxyuridine analogues, and antibodies), (viii) respiratory syncytial virus infections (ribavirin and antibodies), and (ix) external anogenital warts caused by human papillomavirus infections (imiquimod, sinecatechins, and podofilox). Here, we present for the first time a comprehensive overview of antiviral drugs approved over the past 50 years, shedding light on the development of effective antiviral treatments against current and emerging infectious diseases worldwide.

INTRODUCTION

Over the course of human civilization, viral infections have caused millions of human casualties worldwide, driving the development of antiviral drugs in a pressing need (1, 2). A new era of antiviral drug development has begun since the first antiviral drug, idoxuridine, was approved in June 1963 (3) (Fig. 1). Since then, many antiviral drugs have been developed for clinical use to treat millions of human beings worldwide. Between June 1963 and April 2016, 90 drugs were formally approved to treat 9 human infectious diseases (Table 1) despite the fact that thousands of antiviral inhibitors have been proposed in the literature. Previously, we reviewed the history of 25 approved antiretroviral drugs over 25 years (1984 to 2009) (4, 5). The present study commemorates 90 antiviral drugs approved for the treatment of 9 human infectious diseases over the past 5 decades.

Approved antiviral drugs could be arbitrarily divided in 13 functional groups: (i) 5-substituted 2′-deoxyuridine analogues ($n = 3$ drugs and drug combinations); (ii) nucleoside analogues ($n = 3$); (iii) (nonnucleoside) pyrophosphate analogues ($n = 1$); (iv) nucleoside reverse transcriptase (RT) inhibitors (NRTIs) ($n = 9$); (v) nonnucleoside reverse transcriptase inhibitors (NNRTIs) ($n = 5$); (vi) protease inhibitors (PIs) ($n = 19$); (vii) integrase inhibitors ($n = 5$); (viii) entry inhibitors ($n = 7$); (ix) acyclic guanosine analogues ($n = 6$); (x) acyclic nucleoside phosphonate (ANP) analogues ($n = 10$); (xi) hepatitis C virus (HCV) NS5A and NS5B inhibitors ($n = 8$); (xii) influenza virus inhibitors ($n = 8$); and (xiii) immunostimulators, interferons, oligonucleotides, and antimitotic inhibitors ($n = 8$). The inhibitory spectrum of these approved drugs against 9 human infectious diseases can be summarized as follows: human immunodeficiency virus (HIV) (groups iv, v, vi, vii, viii, and x), human cytomegalovirus (HCMV) (groups iii, ix, x, and xiii), hepatitis B virus (HBV) (groups ii, iv, x, and xiii), HCV (groups vi, xi, xii, and xiii), herpes simplex virus (HSV) (groups i, ii, iii, viii, and ix), influenza virus (group xii), respiratory syncytial virus (RSV) (groups viii and xii), varicella-zoster virus (VZV) (groups i, ii, viii, and ix), and human papillomavirus (HPV) (group xiii). Table 2 summarizes the information on antiviral drugs regarding their approval dates and mechanisms of drug action. Table S1 in the supplemental material provides details on drug databases and chemical formulas.

Nine human viruses can be classified into DNA viruses (HBV, HCMV, HSV, HPV, and VZV), RNA viruses (HCV, RSV, and influenza virus), and retroviruses (HIV) (Fig. 2). Interestingly, 11 of 90 antiviral drugs have been approved for the treatment of more

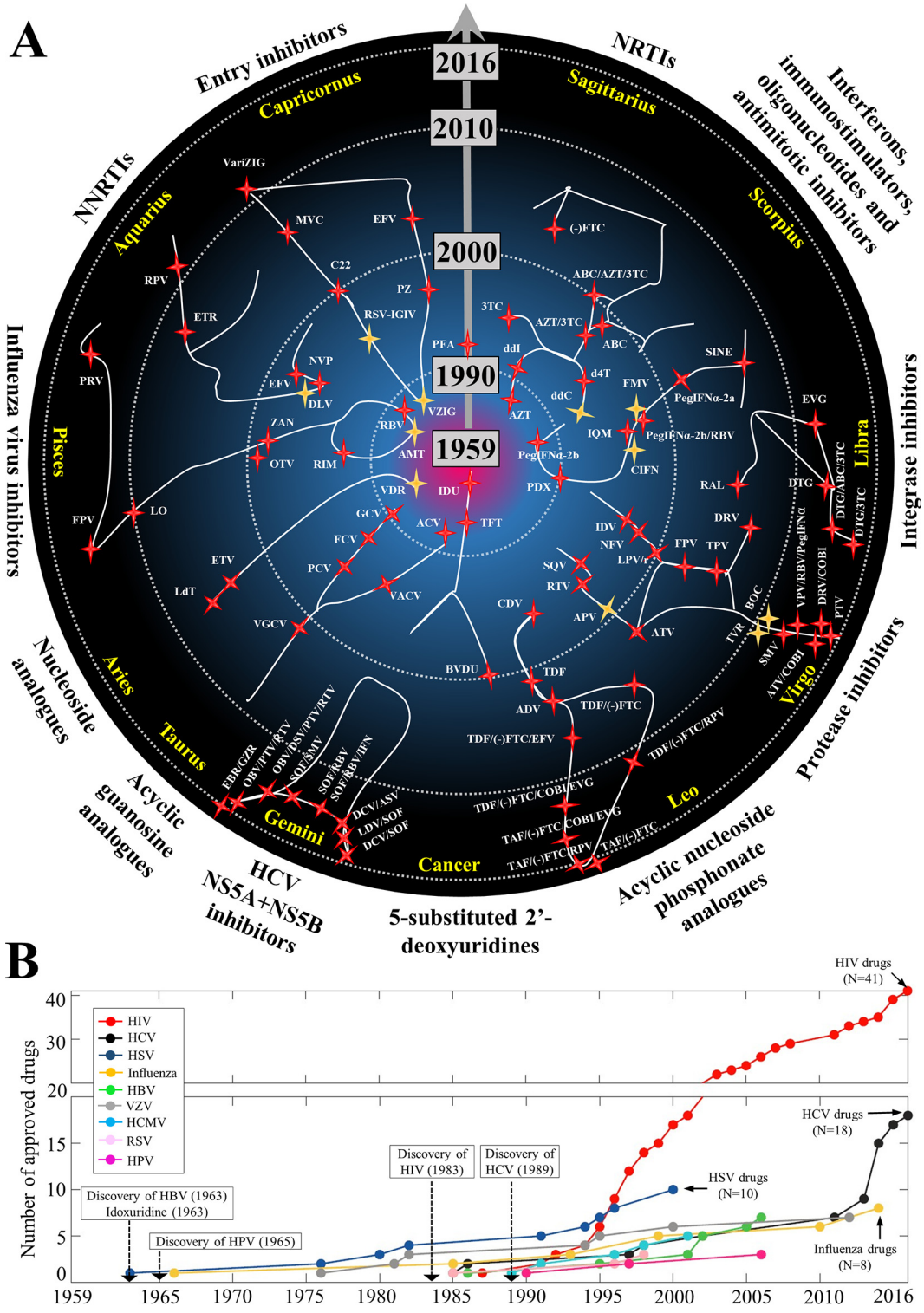

FIG 1 History of antiviral drugs approved between January 1959 and April 2016. (A) Approved antiviral drugs visualized in the zodiac. The gray arrow shows the dates of approval of antiviral drugs from January 1959 to April 2016. Twelve signs are positioned in a circle. Each sign indicates a drug group whose name is annotated outside the circle. In the drug group, each red star within a sign represents an approved drug, placed according to the year of approval. Yellow stars indicate approved drugs that have been discontinued or abandoned for clinical use. A total of 90 stars thus represent all approved antiviral drugs, and each drug star is positioned according to its approval date (Table 2). In this picture, every approved drug could be conceived as a "superstar," and its contribution to human health is worthy of being remembered and respected. Therefore, this zodiac-based figure metaphorically recognizes each antiviral drug as a star in the universe, commemorating the significant contributions of antiviral drug discovery and development over the past 50 years. A list of drug abbreviations is available in Table 2. Movies and label information for approved drugs are accessible online (see http://www.virusface.com/). (B) Timeline of approval of drugs against 9 human infectious diseases (HIV, HBV, HCV, HSV, HCMV, HPV, RSV, VZV, and influenza virus). The *x* axis indicates the period from January 1959 to April 2016, and the *y* axis shows the total number of approved drugs. For each virus, a colored line demonstrates the total number of approved drugs. Moreover, years of discovery of HBV (1963), HPV (1965), HIV (1983), and HCV (1989) are indicated, while the other five viruses were discovered before 1959 (Table 1).

TABLE 1 Summary of 9 human infectious diseases treated by approved drugs

Human virus	Yr of discovery/ isolation	Animal reservoir(s)	Transmission route	Mean incubation period (range)	Mean viral particle diam (nm) (range)	Genome type,[c] length (kb)	Protein target(s) of approved drug(s)
HIV	1983	Chimpanzee, gorilla, sooty mangabey	Blood borne	8–11 yr	~145 (95–166)	Linear (+)ssRNA, ~9.8	Protease, RT, integrase, GP41, CCR5
HCV	1989	Unclear	Blood borne	~7 wk (4–20 wk)	~68 (45–86)	Linear (+)ssRNA, ~9.6	NS3/4 protease, NS5A, NS5B polymerase
Human influenza virus	1933	Birds, pigs, horses	Respiratory	~2 days (1–4 days)	~120 (84–170)	Linear (−)ssRNA, ~13.6	Matrix protein 2, neuraminidase, RNA polymerase
RSV	1957	No animal reservoir	Respiratory	~5 days (3–8 days)	100–1,000	Linear (−)ssRNA, ~15	RNA polymerase, glycoproteins
HBV	1963	Unclear (bats?)	Blood borne	90 days (60–150 days)	42–46	Circular dsDNA, ~3.3	DNA polymerase
HCMV	1956	No animal reservoir	Blood borne	3–12 wk	150–200	Linear dsDNA, ~230	DNA polymerase
HSV	Before 1900	No animal reservoir	Sexual or skin contact	~4 days (2–12 days)	~225 (209–239)	Linear dsDNA, 152–155	DNA polymerase, envelope proteins
VZV	1953	No animal reservoir	Respiratory	10–21 days	150–200	Linear dsDNA, ~125	DNA polymerase, envelope proteins
HPV	1965	No animal reservoir[a]	Skin-to-skin contact	~2.9 mo (0.5–8 mo)	65–120	Circular dsDNA, ~8	—[b]

[a] Papillomaviruses have been widely found in birds, reptiles, marsupials, and mammals, whereas cross-transfer between species is rare (54).
[b] Instead of targeting HPV proteins directly, three FDA-approved drugs (podofilox, sinecatechins, and imiquimod) act as immunomodulatory or antimitotic agents to treat external genital warts caused by HPV infections.
[c] (+)ssRNA, positive-sense single-stranded RNA; (−)ssRNA, negative-sense single-stranded RNA; dsDNA, double-stranded DNA.

than one infectious disease (Table 2), suggesting that antiviral drugs may potentially treat multiple viral infections. Ribavirin, for instance, is effective against three RNA viruses: HCV, RSV, and influenza virus (Fig. 3). More importantly, antiviral drugs from the same drug group share similar mechanisms of drug action to inhibit viral replication during the viral life cycle (Fig. 4). In some cases, approved antiviral drugs could be used as off-label treatments for emerging infectious diseases. Therefore, a comprehensive review that summarizes all approved antiviral drugs will shed light on the development of novel inhibitors against current and emerging viral infections.

In this review, we first give an overview of 9 human viruses. Subsequently, the following three perspectives of 90 approved drugs are discussed. (i) How were they discovered, and against which viral infections are they active? (ii) How do they achieve their mechanisms of action to target viral or host proteins? (iii) What therapeutic aspects do they have? In addition, we make a summary of promising antiviral compounds in phase 3 clinical trials (Table 3). To give a comprehensive overview, we highlight the latest progress on antiviral drugs and vaccines against emerging infectious diseases. Challenges in the field of antiviral drug discovery are envisioned at the end. To support this review, we have also established an online platform (http://www.virusface.com/) to update the therapeutic aspects of antiviral drugs and vaccines.

OVERVIEW OF NINE HUMAN VIRUSES

As of April 2016, antiviral drugs have been approved to treat 9 human infectious diseases (HIV, HBV, HCV, HCMV, HSV, HPV, RSV, VZV, and influenza virus), albeit more than 200 human viruses have been discovered (6). Below, we give an overview of the origins, pathogenicities, epidemiologies, and clinical complications of these 9 human viruses.

Human Immunodeficiency Virus

Discovered in 1983 (7), HIV, a lentivirus in the *Retroviridae* family, is the causative agent of AIDS (8). An HIV particle, which is ~145 nm (range, 95 to 166 nm) in diameter (9), contains a linear single-stranded RNA (ssRNA) genome encoding 15 mature viral proteins (10) (Table 1). HIV strains can be classified into two types (HIV-1 and HIV-2), which are further divided into extensive groups, subtypes, and recombinant forms (for a review, see reference 11). A high level of genetic variation has been observed in the HIV genome, making HIV one of the fastest-evolving organisms (12). It has been estimated that the nucleotide diversity of HIV genomes is almost 50% between HIV-1 and HIV-2, 37.5% between HIV-1 groups, and 14.7% between HIV-1 subtypes (10). Regarding the origin of HIV, it can be traced to West Central Africa in the late 19th or the early 20th century, when the butchering and consumption of primate bushmeat were widely practiced (11, 13). Due to multiple zoonotic transfers, HIV is known to be transmitted from chimpanzees (HIV-1 groups M and N), gorillas (HIV-1 groups P and O), and sooty mangabeys (HIV-2) to humans (11, 14–16) (Fig. 2). As a blood-borne virus, HIV is spread mainly through HIV-contaminated blood or body fluids; thereby, patients can become infected with HIV by sexual contact, needle sharing, blood transfusions, or maternal transmissions. During chronic infection, the incubation period of HIV can be 8 to 11 years (17). Many clinical complications have been reported: lymphoma, psychiatric disorders, gingivitis, cardiovascular disease, lung cancer, kidney disease, osteoporosis, papulosquamous

disorders, and dental or salivary gland diseases (for a review, see reference 18). In the past 3 decades, HIV has caused a great burden to global wealth and health. According to the WHO global health survey, ~36.9 million (range, 34.3 million to 41.4 million) people were infected with HIV, causing 1.2 million (range, 1.0 million to 1.5 million) deaths in 2014.

Hepatitis C Virus

Discovered in 1989 (19), HCV is a hepacivirus in the *Flaviviridae* family (Fig. 2). An HCV particle, which is ~68 nm (range, 45 to 86 nm) in diameter (20), contains a linear, positive-sense, single-stranded RNA genome encoding 10 viral proteins (21). HCV strains can be classified into 7 major genotypes (genotypes 1 to 7), among which genotypes 1 and 2 cause most infections worldwide (22). It has been estimated that the nucleotide diversity of HCV genomes is about 32.4% between HCV genotypes and 14.6% within HCV genotypes (23). Regarding the origin of HCV, it remains a mystery, but nonhuman primates (apes and monkeys) and mammals (e.g., horses and dogs) might have been potential zoonotic reservoirs (24). As a blood-borne virus, HCV is transmitted mainly by sexual contact, needle sharing, blood transfusions, or maternal transmissions. During acute infection, the incubation period of HCV is ~7 weeks (range, 4 to 20 weeks) (25). Many clinical complications have been observed, including liver cirrhosis, liver failure, portal hypertension, or hepatocellular carcinoma (26, 27). HCV is also known to cause liver cancers such as hepatocellular carcinoma (28). According to the WHO global health survey, HCV causes 500,000 deaths every year, and 130 million to 150 million people were living with HCV in 2014.

Influenza Virus

Human influenza viruses from the *Orthomyxoviridae* family (Fig. 2) caused the first recognizable influenza pandemic in the summer of 1510 (29, 30), and they were isolated for the first time in 1933 (31). A viral particle of influenza virus, which is ~120 nm (range, 84 to 170 nm) in diameter (32), contains a linear, negative-sense, single-stranded RNA genome that encodes 11 or 12 proteins depending on the virus strain (33). Influenza viruses can be classified into three types: types A, B, and C. Influenza A viruses that cause human epidemics and pandemics (e.g., Spanish flu in 1918, Asian flu in 1957, and Hong Kong flu in 1968) are further divided into extensive subtypes (i.e., H1N1, H1N2, or H3N2) based on the sequence variation of hemagglutinin (HA) and neuraminidase (NA), two glycoproteins of the influenza virus membrane (34, 35). Influenza B viruses that cause human epidemics are divided into strains but not subtypes. Influenza C viruses cause neither epidemics nor pandemics, because they usually infect humans with mild illnesses. On the other hand, influenza viruses have been discovered in a broad spectrum of animal reservoirs (36). Influenza A viruses can be transmitted from animal reservoirs such as birds (e.g., H2N2, H5N1, H7N3, and H9N2), pigs (e.g., H1N1 and H3N2), or seals (H7N7) to humans (36). Using respiratory routes, influenza viruses spread mostly through direct contact with contaminated aerosols or droplets. During influenza infection, the typical incubation period is ~1 to 4 days (average, 2 days), and many clinical complications (e.g., pneumonia, bronchitis, dehydration, encephalitis, sinusitis, and ear infections) have been reported (see http://www.cdc.gov/). According to the WHO global health survey, influenza viruses cause 250,000 to 500,000 deaths every year, and 3 million to 5 million cases of severe illnesses were reported in 2014.

Respiratory Syncytial Virus

Discovered in 1957 (37), human RSV belongs to the *Pneumovirus* genus in the *Paramyxoviridae* family (Fig. 2). An RSV particle, which is ~100 to 1,000 nm in diameter (38), contains a linear, negative-sense, single-stranded RNA genome encoding 11 viral proteins (39). RSV strains can be classified into two antigenic subtypes, subtypes A and B, which are further divided into 11 RSV-A and 23 RSV-B genotypes (40). Similar to influenza viruses, RSV takes respiratory routes for its transmission, mainly by direct contact with contaminated aerosols or droplets. Nevertheless, there is no animal reservoir for human RSV (41). During human RSV infection, the incubation period is ~5 days (range, 3 to 8 days) (42), and many clinical complications (e.g., respiratory tract diseases, sinusitis, otitis bronchiolitis, and pneumonia) have been observed (see http://www.cdc.gov/). Regarding the burden of RSV, it causes 66,000 to 199,000 deaths every year. In 2005, RSV infections caused 33.8 million cases of RSV-associated acute lower respiratory infections among children <5 years of age (43).

Hepatitis B Virus

Discovered in 1963 (44), HBV belongs to the *Orthohepadnavirus* genus in the *Hepadnaviridae* family (Fig. 2). An HBV particle, which is ~42 to 46 nm in diameter (45), contains a circular double-stranded DNA (dsDNA) genome encoding 6 viral proteins. HBV strains have been classified into 8 genotypes, further divided into more than 24 subtypes. It has been estimated that the nucleotide diversity of HBV genomes is ~14.5% between HBV genotypes and 2.8% within HBV genotypes (46). Regarding the origin of HBV, it remains a mystery to be unveiled, but bats might have been the ancestral sources of primate hepadnaviruses (47, 48). As a blood-borne virus, HBV can be transmitted by sexual contact, needle sharing, blood transfusions, or maternal transmissions. The incubation period of HBV infections is ~90 days (range, 60 to 150 days) (49). Major clinical complications of HBV infections have been observed, such as hepatitis, anorexia, abdominal discomfort, nausea, vomiting, arthralgia, rash, or liver cancer (see http://www.cdc.gov/). HBV is also known to cause liver cancers (e.g., hepatocellular carcinoma) (28). According to the WHO global health survey, HBV causes 780,000 deaths every year, and 240 million people were infected in 2014.

Human Papillomavirus

Discovered in 1965 (50), HPVs from the *Papillomaviridae* family are the causative agents of >90% of cervical cancers, the second most common cancer among women worldwide (51). An HPV particle, which is ~65 to 120 nm in diameter (52), contains a closed, circular, double-stranded DNA genome encoding 9 viral proteins (53). HPV strains can be classified into >200 types based on the sequence variation of a late region encoding the capsid protein L1 (54). HPV infections are responsible for ~5% of human cancers (e.g., cervical carcinoma, anal carcinoma, and penile carcinoma) (28, 55). Particularly, high-risk HPV type 16 (HPV-16) and HPV-18 are known to cause 70% of cervical cancers, while low-risk HPV-6 and HPV-11 cause 90% of external genital warts (56) as well as most cases of recurrent respiratory papillomatosis (57). Papillomaviruses have been widely found in birds, reptiles, marsupials, and mammals, but cross-transfer between species is rare (54). The incubation period from HPV infection to clinical warts varies, and the average time is ~2.9 months (range, 0.5 to 8 months) (58). HPV infections are transmitted mainly through

TABLE 2 Summary of 90 approved antiviral drugs in 13 drug groups[f]

Drug group	Drug name	Abbreviation[c]	Brand name(s)[d]	Approved clinical use(s)	Mechanism(s) of drug action	Approval date[e]
5-substituted 2′-deoxyuridine analogues	Idoxuridine	IDU	Dendrid	HSV-1	Substitutes for thymidine and targets HSV DNA polymerase to inhibit viral DNA synthesis	June 1963
	Trifluridine	TFT	Viroptic	HSV	Inhibits HSV DNA replication	Apr. 1980
	Brivudine	BVDU	Zostex (Europe)	HSV-1, VZV	Brivudine triphosphate targets VZV DNA polymerase to inhibit viral DNA synthesis	2000
Nucleoside analogues	Vidarabine[a]	VDR	Vira-A	HSV, VZV	Vidarabine triphosphate competes with dATP to inhibit the activity of viral DNA polymerase	Nov. 1976
	Entecavir	ETV	Baraclude	HBV	Inhibits the activity of HBV DNA polymerase	Mar. 2005
	Telbivudine	LdT	Tyzeka	HBV	Inhibits the activity of HBV DNA polymerase	Oct. 2006
Pyrophosphate analogues	Foscarnet	PFA	Foscavir	HCMV, HSV (acyclovir resistant)	Inhibits the activity of viral DNA polymerase	Sept. 1991
NRTIs	Zidovudine	AZT	Retrovir	HIV	Targets HIV RT and competes with dTTP to inhibit DNA synthesis	Mar. 1987
	Didanosine	ddI	Videx	HIV	Targets HIV RT and competes with dATP to inhibit DNA synthesis	Oct. 1991
	Zalcitabine[a]	ddC	Hivid	HIV	Targets HIV RT and competes with dCTP to inhibit DNA synthesis	June 1992
	Stavudine	d4T	Zerit	HIV	Targets HIV RT and competes with dTTP to inhibit DNA synthesis	June 1994
	Lamivudine	3TC	Epivir	HIV, HBV	Targets viral polymerase and competes with dCTP to inhibit DNA synthesis	Nov. 1995
	Lamivudine + zidovudine	3TC+AZT	Combivir	HIV	Twice-daily, fixed-dose, single-tablet drug used to inhibit the activity of HIV RT	Sept. 1997
	Abacavir	ABC	Ziagen	HIV	Targets HIV RT and competes with dGTP to inhibit DNA synthesis	Dec. 1998
	Abacavir + lamivudine + zidovudine	ABC+3TC+AZT	Trizivir	HIV	Twice-daily, fixed-dose, single-tablet drug of abacavir, lamivudine, and zidovudine used to inhibit the activity of HIV RT	Nov. 2000
	Emtricitabine	(−)FTC	Emtriva	HIV	Targets HIV RT and competes with dCTP to inhibit DNA synthesis	July 2003
NNRTIs	Nevirapine	NVP	Viramune	HIV-1	Binds directly to HIV RT and inhibits DNA synthesis	June 1996
	Delavirdine[a]	DLV	Rescriptor	HIV-1	Binds directly to HIV RT and inhibits DNA synthesis	Apr. 1997
	Efavirenz	EFV	Sustiva	HIV-1	Binds directly to HIV RT and inhibits DNA synthesis	Sept. 1998

	Etravirine	ETR	Intelence	HIV-1	Binds directly to HIV RT and inhibits DNA synthesis	Jan. 2008
	Rilpivirine	RPV	Edurant	HIV-1	Binds directly to HIV RT and inhibits DNA synthesis	Aug. 2011
Protease inhibitors	Saquinavir	SQV	Invirase	HIV	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins	Dec. 1995
	Ritonavir	RTV	Norvir	HIV	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins	Mar. 1996
	Indinavir	IDV	Crixivan	HIV	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins	Mar. 1996
	Nelfinavir	NFV	Viracept	HIV	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins	Mar. 1997
	Amprenavir[a]	APV	Agenerase	HIV-1	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins	Apr. 1999
	Lopinavir-ritonavir	LPV/r	Kaletra	HIV	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins	Sept. 2000
	Atazanavir	ATV	Reyataz	HIV	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins	June 2003
	Fosamprenavir	FPV	Lexia	HIV-1	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins	Oct. 2003
	Tipranavir	TPV	Aptivus	HIV-1	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins	June 2005
	Darunavir	DRV	Prezista	HIV	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins	June 2006
	Darunavir + cobicistat	DRV+COBI	Prezcobix	HIV	HIV protease inhibitors can be combined with cobicistat to inhibit the activity of HIV protease	Jan. 2015
	Atazanavir + cobicistat	ATV+COBI	Evotaz	HIV		Jan. 2015
	Telaprevir[a]	TVR	Incivek	HCV genotype 1	HCV protease drugs can inhibit the proteolytic activity of HCV NS3/4A protease; ribavirin and PegIFNα can interfere with HCV replication	May 2011
	Boceprevir[a]	BOC	Victrelis	HCV genotype 1		May 2011
	Simeprevir	SMV	Olysio	HCV genotype 1		Nov. 2013
	Asunaprevir[b]	ASV	Sunvepra (Japan)	HCV genotype 1		July 2014
	Vaniprevir + ribavirin + PegIFNα-2b	VPV+RBV+PegIF-α2b	Vanihep (Japan)	HCV genotype 1		Sept. 2014

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TABLE 2 (Continued)

Drug group	Drug name	Abbreviation[c]	Brand name(s)[d]	Approved clinical use(s)	Mechanism(s) of drug action	Approval date[e]
	Paritaprevir[b]	PTV	Viekira Pak	HCV genotype 1		Dec. 2014
			Technivie	HCV genotype 4		July 2015
	Grazoprevir[b]	GZR	Zepatier	HCV genotype 1 or 4		Jan. 2016
Integrase inhibitors	Raltegravir	RAL	Isentress	HIV	Targets HIV integrase to inhibit the integration of viral DNA into human chromosomes	Oct. 2007
	Elvitegravir	EVG	Vitekta	HIV	Targets HIV integrase to inhibit the integration of viral DNA into human chromosomes	Aug. 2012
	Dolutegravir	DTG	Tivicay	HIV	Targets HIV integrase to inhibit the integration of viral DNA into human chromosomes	Aug. 2013
	Dolutegravir + abacavir + lamivudine	DTG+ABC+3TC	Triumeq	HIV	Fixed-dose combinations with dolutegravir and NRTIs can target HIV integrase and RT to interrupt viral replication	Aug. 2014
	Dolutegravir + lamivudine	DTG+3TC	Dutrebis	HIV		Feb. 2015
Entry inhibitors	RSV-IGIV[a]	RSV-IGIV	RespiGam	RSV	RSV-neutralizing antibodies may prevent binding of RSV surface glycoproteins F and G	Jan. 1996
	Palivizumab	PZ	Synagis	RSV	Monoclonal antibody that targets the antigenic site of RSV glycoprotein F	June 1998
	Docosanol	C22	Abreva	HSV	May interfere with binding of viral envelope proteins to cell membrane receptors	July 2000
	Enfuvirtide	EFV	Fuzeon	HIV-1	Blocks HIV GP41 fusion to cell membrane	Mar. 2003
	Maraviroc	MVC	Selzentry	HIV	Blocks GP120-CCR5 interaction to inhibit HIV entry	Aug. 2007
	VZIG[a]	VZIG	VZIG	VZV	IgG antibodies protect patients from VZV infection	Feb. 1981
	VariZIG	VariZIG	VariZIG	VZV	IgG antibodies protect patients from VZV infection	Dec. 2012
Acyclic guanosine analogues	Acyclovir	ACV	Zovirax	HSV, VZV	Acyclovir triphosphate competes with dGTP to inhibit viral DNA polymerase activity	Mar. 1982
	Ganciclovir	GCV	Zirgan, Vitrasert	HCMV	Ganciclovir triphosphate targets HCMV DNA polymerase to inhibit viral DNA synthesis	June 1989
	Famciclovir	FCV	Famvir	HSV, VZV	Famciclovir triphosphate competes with dGTP to inhibit the activity of viral DNA polymerase	June 1994

	Valacyclovir	VACV	Valtrex	HSV, VZV	Valacyclovir triphosphate competes with dGTP to inhibit the activity of viral DNA polymerase	June 1995
	Penciclovir	PCV	Denavir	HSV	Penciclovir triphosphate targets HSV DNA polymerase to inhibit viral DNA synthesis	Sept. 1996
	Valganciclovir	VGCV	Valcyte	HCMV	Valganciclovir triphosphate competes with dGTP to inhibit the activity of viral DNA polymerase	Mar. 2001
Acyclic nucleoside phosphonate analogues	Cidofovir	CDV	Vistide	HCMV retinitis (AIDS patients)	Inhibits the activity of HCMV DNA polymerase	June 1996
	Tenofovir disoproxil fumarate	TDF	Viread	HIV, HBV	Competes with dATP to inhibit the activity of HIV RT and HBV DNA polymerase	Oct. 2001
	Adefovir dipivoxil	ADV	Hepsera	HBV	Adefovir diphosphate competes with dATP to inhibit the activity of HBV DNA polymerase	Sept. 2002
	Tenofovir disoproxil fumarate + emtricitabine	TDF+(−)FTC	Truvada	HIV	Truvada is a once-daily fixed-dose single tablet containing 2 drugs to inhibit HIV replication	Aug. 2004
	Tenofovir disoproxil fumarate + efavirenz + emtricitabine	TDF+EFV+(−)FTC	Atripla	HIV	Atripla is a once-daily fixed-dose single tablet containing 3 drugs to inhibit HIV replication	July 2006
	Tenofovir disoproxil fumarate + rilpivirine + emtricitabine	TDF+RPV+(−)FTC	Complera, Eviplera	HIV	Complera is a once-daily fixed-dose single tablet containing 3 drugs to inhibit HIV replication	Aug. 2011
	Tenofovir disoproxil fumarate + cobicistat + emtricitabine + elvitegravir	TDF+COBI+(−)FTC+EVG	Stribild	HIV	Stribild is a once-daily fixed-dose single tablet containing 4 drugs to inhibit HIV replication	Aug. 2012
	Tenofovir alafenamide + cobicistat + emtricitabine + elvitegravir	TAF+COBI+(−)FTC+EVG	Genvoya	HIV	Genvoya is a once-daily fixed-dose single tablet containing 4 drugs to inhibit HIV replication	Nov. 2015
	Tenofovir alafenamide + rilpivirine + emtricitabine	TAF+RPV+(−)FTC	Odefsey	HIV	Odefsey is a once-daily fixed-dose single tablet containing 3 drugs to inhibit HIV replication	Mar. 2016
	Tenofovir alafenamide + emtricitabine	TAF+(−)FTC	Descovy	HIV	Descovy is a once-daily fixed-dose single tablet containing 2 drugs to inhibit HIV replication	Apr. 2016
HCV NS5A and NS5B inhibitors	Sofosbuvir + ribavirin	SOF+RBV	Sovaldi	HCV genotype 2 or 3	Sofosbuvir binds to Mg^{2+} ions in NS5B polymerase and inhibits HCV replication; ribavirin and PegIFNα can interfere with HCV replication	Dec. 2013
	Sofosbuvir + ribavirin + PegIFNα	SOF+RBV+PegIFNα	Sovaldi	HCV genotype 1 or 4		Dec. 2013

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TABLE 2 (Continued)

Drug group	Drug name	Abbreviation[c]	Brand name(s)[d]	Approved clinical use(s)	Mechanism(s) of drug action	Approval date[e]
	Daclatasvir + asunaprevir	DCV+ASV	Daklinza + Sunvepra (Japan)	HCV genotype 1	Targets NS5A and NS3/4A protease to prevent HCV replication	July 2014
	Ledipasvir + sofosbuvir	LDV+SOF	Harvoni	HCV genotype 1	Harvoni inhibits HCV NS5A and NS5B polymerase to prevent RNA replication	Oct. 2014
	Sofosbuvir+ simeprevir	SOF+SMV	Sovaldi + Olysio	HCV genotype 1	Sofosbuvir and simeprevir target HCV NS5B and NS3/4 protease, respectively	Nov. 2014
	Ombitasvir + dasabuvir + paritaprevir + ritonavir	OBV+DAS+PTV+RTV	Viekira Pak	HCV genotype 1	Viekira Pak is a multiclass combination drug approved for treatment of HCV genotype 1 infection; inhibits activities of HCV NS5A, NS5B polymerase, and NS3/4A protease	Dec. 2014
	Ombitasvir + paritaprevir + ritonavir	OBV+PTV+RTV	Technivie	HCV genotype 4	Technivie is used with ribavirin to treat HCV genotype 4 infection; inhibits HCV NS5A and NS3/4A protease	July 2015
	Daclatasvir + sofosbuvir	DCV+SOF	Daklinza + Sovaldi	HCV genotype 3	Inhibits activities of HCV NS5A and NS5B polymerase	July 2015
	Elbasvir + grazoprevir	EBR+GZR	Zepatier	HCV genotype 1 or 4	Elbasvir and grazoprevir inhibit activities of NS5A and NS3/4A protease, respectively	Jan. 2016
Influenza virus inhibitors	Amantadine[a]	AMT	Symmetrel	Influenza virus A	Targets viral matrix protein 2 to inhibit viral uncoating	Oct. 1966
	Ribavirin	RBV	Copegus, Rebetol, Virazole	HCV, RSV, hemorrhagic fever	Ribavirin triphosphate targets viral RNA polymerase to inhibit mRNA synthesis	Dec. 1985
	Rimantadine	RIM	Flumadine	Influenza virus A	Targets matrix protein 2 to inhibit viral uncoating	Sept. 1993
	Zanamivir	ZAN	Relenza	Influenza viruses A and B	Targets viral neuraminidase to inhibit virus release from host cells	July 1999
	Oseltamivir	OTV	Tamiflu	Influenza viruses A and B	Targets viral neuraminidase to inhibit virus release from host cells	Oct. 1999
	Laninamivir octanoate	LO	Inavir (Japan)	Influenza viruses A and B	Targets viral neuraminidase to inhibit virus release from host cells	Sept. 2010
	Peramivir	PRV	Rapivab	Influenza viruses A and B	Targets viral neuraminidase to inhibit virus release from host cells	Dec. 2014
	Favipiravir	FPV	Avigan (Japan)	Influenza viruses A, B, and C	Favipiravir-ribofuranosyl-5′-triphosphate inhibits the activity of influenza RNA polymerase	Mar. 2014
Interferons, immunostimulators, oligonucleotides, and antimitotic inhibitors	Pegylated interferon alfa 2b	PegIFNα-2b	Intron-A, PegIntron	HBV, HCV	PegIFNα-2b is used to treat patients with HBV and/or HCV infection	June 1986
	Interferon alfacon 1[a]	CIFN	Infergen	HCV genotype 1	Interferon alfacon 1 can be used with ribavirin to treat HCV infection	Oct. 1997
	Pegylated interferon alfa 2b + ribavirin	PegIFNα-2b+RBV	Rebetron	HCV	PegIFNα-2b is used with ribavirin to treat patients with HCV infection	June 1998

Pegylated interferon alfa 2a	PegIFN-α2a	Pegasys, Roferon-A	HBV, HCV	Used with or without ribavirin to treat patients with HCV and/or HBV infection	Oct. 2002
Fomivirsen[a]	FMV	Vitravene	HCMV	Antisense RNA interrupts HCMV gene expression	Aug. 1998
Podofilox	PDX	Condylox	HPV-related diseases	Antimitotic drug that interrupts cell division	Dec. 1990
Imiquimod	IQM	Aldara	HPV-related diseases	Stimulates cytokines to clear external genital warts	Feb. 1997
Sinecatechins	SINE	Veregen	HPV-related diseases	Botanical drug that acts as an immunomodulator to interfere with HSV-induced pathways	Oct. 2006

[a] Discontinued antiviral drug (amantadine, amprenavir, boceprevir, delavirdine, fomivirsen, RSV-IGIV, VZIG, telaprevir, vidarabine, zalcitabine, and interferon alfacon 1).
[b] Different combination drugs. The combination of asunaprevir plus daclatasvir was approved to treat HCV genotype 1 infection in Japan, the combination of grazoprevir plus elbasvir was approved to treat HCV genotype 1 or 4 infection, the combination of paritaprevir plus ombitasvir plus ritonavir was approved to treat HCV genotype 1 infection, and the combination of paritaprevir plus ombitasvir plus ritonavir was approved to treat HCV genotype 4 infection.
[c] Abbreviations commonly used in literature. The first four letters are used if drug abbreviations could not be found (e.g., sinecatechins are abbreviated SINE).
[d] Antiviral drugs that have been approved in either Japan or Europe but not in the United States are indicated by "(Japan)" or "(Europe)."
[e] Only the earliest time is listed if several approval dates for different clinical applications were found.
[f] Table S1 in the supplemental material summarizes information on drug databases and chemical formulas. Information on dosage and administration of approved antiviral drugs is available online (see http://www.fda.gov/ and http://www.virusface.com/).

intimate skin-to-skin contact. Regarding epidemiology, the worldwide prevalence of HPV in women without cervical abnormalities is ~11% to 12% (59), and HPV is responsible for cervical cancers, causing 266,000 deaths and 528,000 new cases in 2012 (see http://www.who.int/).

Human Cytomegalovirus

Discovered in 1956 (60), HCMV belongs to the *Cytomegalovirus* genus in the *Herpesviridae* family (Fig. 2). An HCMV particle, which is ~150 to 200 nm in diameter (61), contains a linear double-stranded DNA genome harboring ~200 to 250 open reading frames (62). HCMV strains can be classified into four genotypes (gB1, gB2, gB3, and gB4) based on the sequence variation of the UL55 gene encoding glycoprotein B (gB) (63). In the absence of any animal reservoir, HCMV circulates exclusively in human populations (64). As a blood-borne virus, HCMV can be transmitted through blood transfusions, body fluids, breastfeeding, organ transplants, or sexual contact. Notably, the incubation period of HCMV infections is ~3 to 12 weeks. During HCMV infections, many clinical complications have been observed, such as gastrointestinal diseases, mononucleosis, carditis, colitis, antigenemia, ependymitis, esophagitis, encephalitis, retinitis, hepatitis, nephritis, pancreatitis, pneumonia, allograft infections, or central nervous system diseases (65, 66). Moreover, HCMV infections are associated with high morbidity and mortality rates in solid-organ transplant and hematopoietic stem cell transplant recipients (67, 68). Regarding epidemiology, the seroprevalence of HCMV in worldwide populations is between 30% and 95% (69), the percentage of symptomatic children with permanent sequelae is ~40% to 58% (70), and the prevalence of congenital HCMV at birth is estimated to be 0.64% (range, 0.60 to 0.69%) (71).

Herpes Simplex Virus

Discovered before 1900 (72), HSV belongs to the *Simplexvirus* genus in the *Herpesviridae* family (Fig. 2). An HSV particle, which is ~225 nm (range, 209 to 239 nm) in diameter (61), contains a linear double-stranded DNA genome carrying 84 genes (73). HSV can be classified into two types: HSV-1 and HSV-2. The former leads to the majority of cases of oral herpes infections that cause skin lesions and cold sores. The latter is mainly responsible for genital herpes infections that cause pain during urination and blistering sores. In the absence of any animal reservoir, HSV circulates exclusively in human populations (74). HSV-1 transmissions are mediated by direct exposure to contaminated aerosols or droplets, such as oral-to-oral and skin-to-skin contacts. HSV-2 is transmitted mainly by direct exposure to genital skin or fluids of HSV-infected patients. During viral infections, the incubation period of HSV-1 or HSV-2 is ~4 days (range, 2 to 12 days) (75). HSV-1 usually causes pneumonia, keratitis, encephalitis, or orofacial blisters, while HSV-2 typically causes meningitis or genital lesions (74). According to the WHO global health survey, in 2012, 140 million and 417 million people between 15 and 49 years of age lived with HSV-1 and HSV-2, respectively.

Varicella-Zoster Virus

Isolated in tissue culture for the first time in 1953 (76), VZV belongs to the *Varicellovirus* genus in the *Herpesviridae* family (Fig. 2). A VZV particle, which is ~150 to 200 nm in diameter (77), contains a linear double-stranded DNA genome carrying 73 genes (78). VZV strains can be classified into five clades, clades 1 to 5,

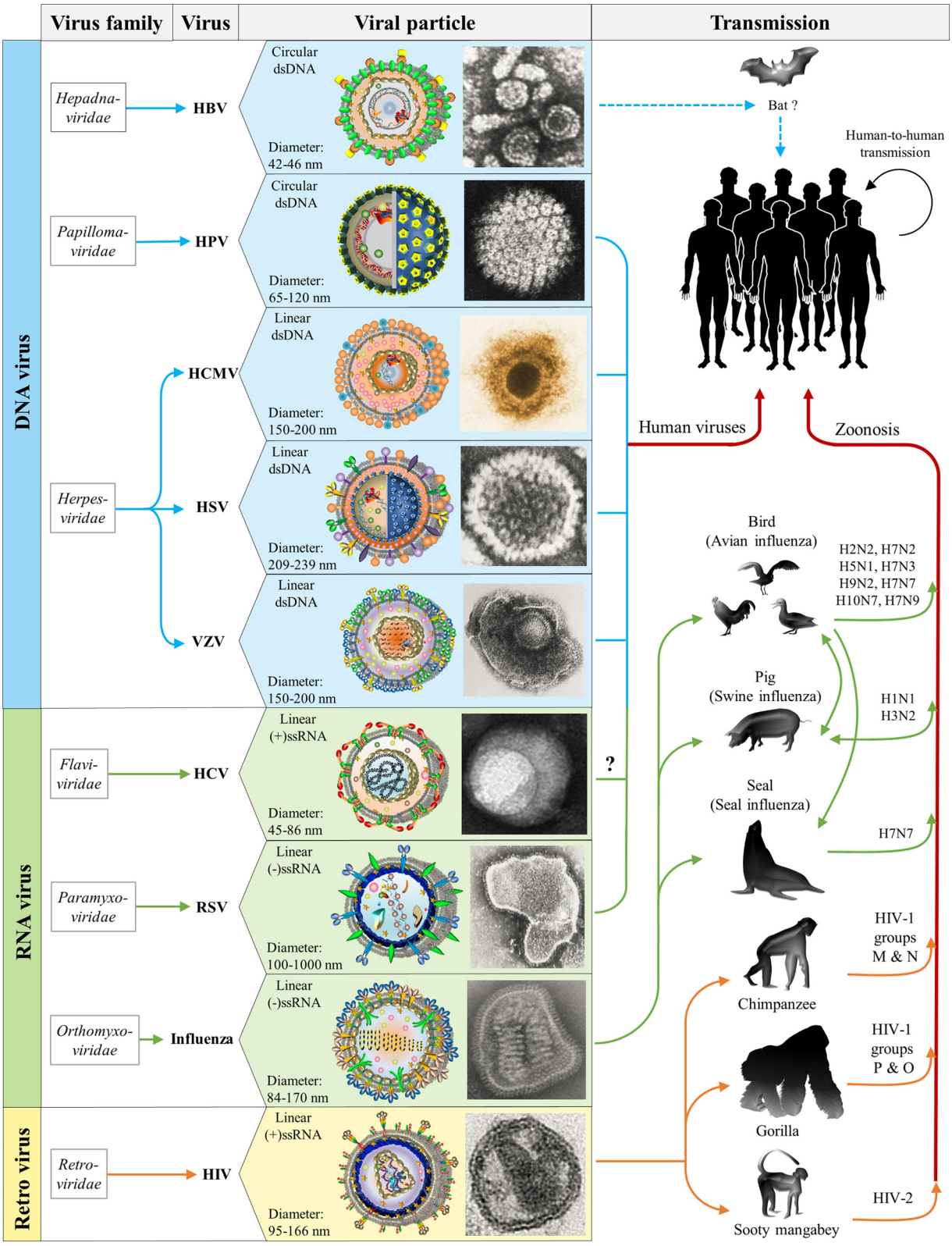

FIG 2 Virus family, morphology, and transmission of HIV, HBV, HCV, HSV, HCMV, HPV, RSV, VZV, and influenza virus. Nine human viruses are classified into DNA viruses (HBV, HCMV, HSV, HPV, and VZV), RNA viruses (HCV, RSV, and influenza virus), and retroviruses (HIV). These viruses are from 7 families: the *Hepadnaviridae* (HBV), the *Papillomaviridae* (HPV), the *Herpesviridae* (HCMV, HSV, and VZV), the *Flaviviridae* (HCV), the *Paramyxoviridae* (RSV), the *Orthomyxoviridae* (influenza virus), and the *Retroviridae* (HIV). Schematic views and electron micrograph images of viral particles are illustrated in boxes, where particle sizes measured as diameters and viral genome types (circular/linear dsDNA or linear RNA) are also indicated (Table 1). Human viruses are further characterized with the possible animal reservoirs. HIV is known to be transmitted from chimpanzees (HIV-1 groups M and N), gorillas (HIV-1 groups P and O),

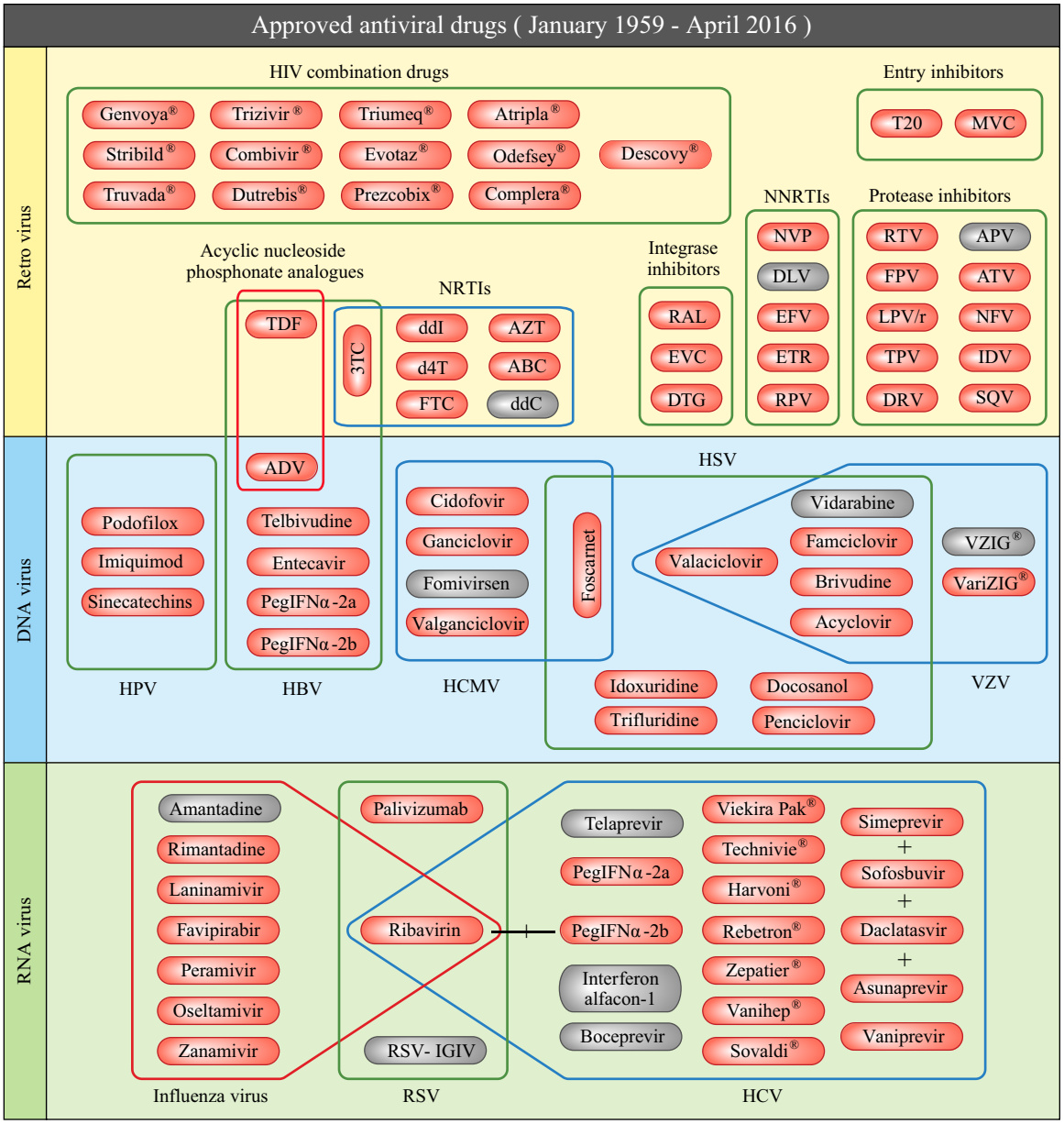

FIG 3 Antiviral drug groups for the treatment of 9 infectious diseases. Approved antiviral drugs are grouped for RNA viruses (HCV, RSV, and influenza virus), DNA viruses (HCMV, HBV, HPV, HSV, and VZV), and retroviruses (HIV). Names of antiviral drugs that are currently in use are enclosed in orange oblongs. Names of discontinued or abandoned antiviral drugs are enclosed in gray oblongs. Those drugs that inhibit more than one virus are shown in the overlapping regions between virus groups. For HCV drugs, a plus symbol is used to indicate the approved combination drugs (simeprevir plus sofosbuvir, sofosbuvir plus daclatasvir, daclatasvir plus asunaprevir, and ribavirin plus PegIFNα-2b).

which are further divided into 9 genotypes (78, 79). In the absence of any animal reservoir, VZV circulates exclusively in human populations (80). VZV is transmitted mostly by respiratory routes, such as by direct contact with respiratory tract secretions (e.g., aerosols and droplets) or lesions. VZV infections, whose incubation period is ~10 to 21 days (81), are known to cause chickenpox as well as a painful skin rash called shingles or herpes zoster (82). Many clinical complications of herpes zoster in immunocompe-

or sooty mangabeys (HIV-2) (11, 14, 15). Influenza viruses that infect humans originate mostly from birds, pigs, or seals (36, 401). Although the origin of HBV has yet to be clarified, bats might be a potential reservoir for HBV (47). HPV has been widely found in birds, reptiles, marsupials, and mammals, but cross-transfer between species is rare (54). Four human viruses (RSV [41], HCMV [64], HSV [74], and VZV [80]) circulate only in human populations and do not have any animal reservoir. In addition, it remains unclear whether HCV has any animal reservoir (27, 476). (The HCV electron micrograph image is republished from reference 20 with permission of the publisher. The HPV electron micrograph image was obtained from the Laboratory of Tumor Virus Biology at the National Cancer Institute [https://visualsonline.cancer.gov/]. The electron micrograph images for HBV, HCMV [by Sylvia Whitfield], HSV [by Fred Murphy and Sylvia Whitfield], VZV [by Erskine L. Palmer and B. G. Partin], RSV [by Erskine L. Palmer], influenza virus [by Erskine L. Palmer and M. L. Martin], and HIV [by Maureen Metcalfe and Tom Hodge] were obtained from the Centers for Disease Control and Prevention [http://phil.cdc.gov/phil/home.asp].)

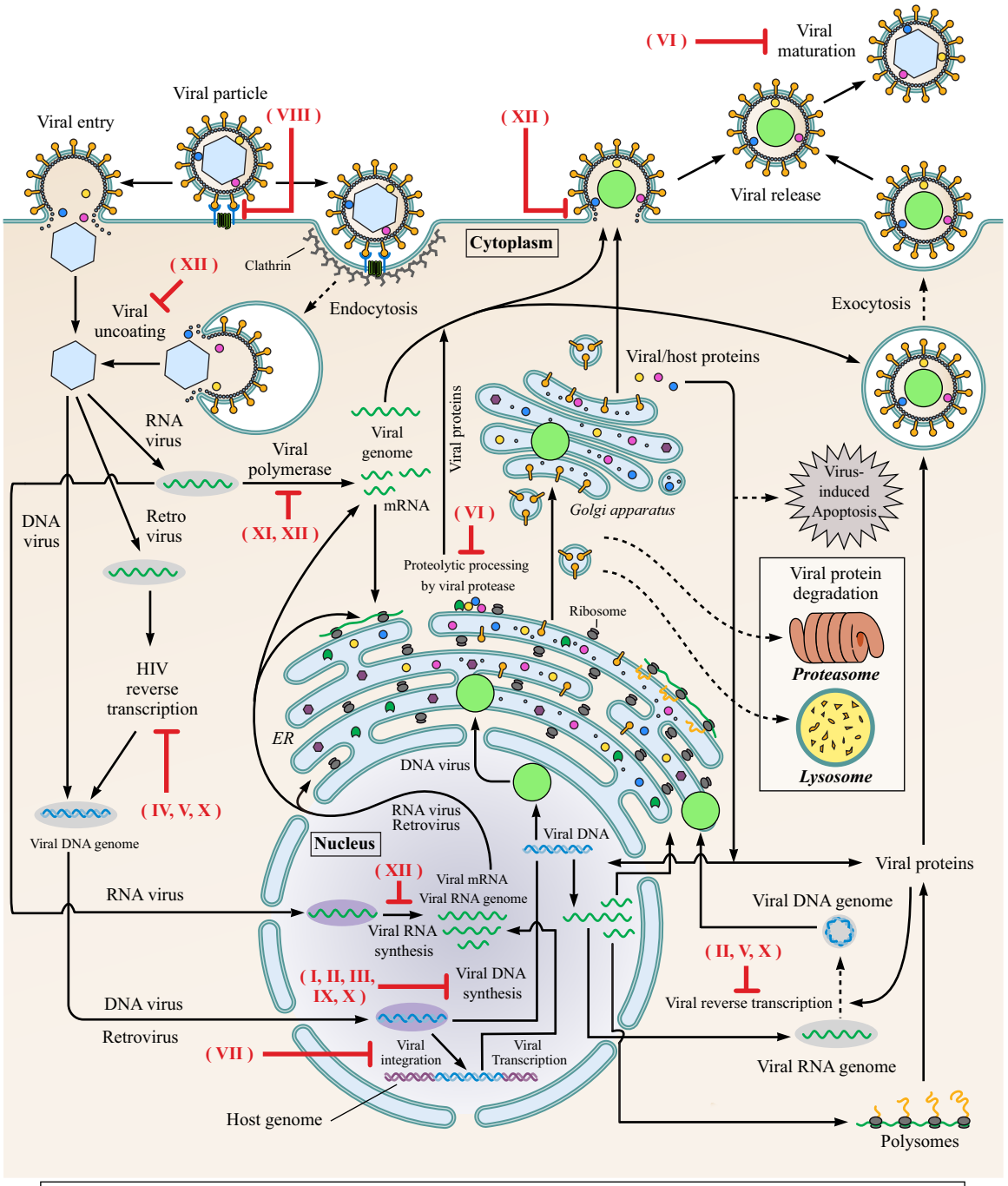

FIG 4 Mechanisms of drug actions during the viral life cycle. Twelve drug groups ordered by roman numerals are shown at the bottom, and their drug actions that interfere with major stages of the viral life cycle are highlighted by red arrows. Solid black arrows indicate direct biological pathways involving viral replication, and dotted black arrows indicate biological pathways with intermediate pathways inside host cells. Major viral stages are illustrated, including endocytosis, exocytosis, virus entry, reverse transcription, virus integration, viral transcription, viral translation, virus budding/release, virus maturation, and other pathways associated with cellular compartments (Golgi apparatus, mitochondria, endoplasmic reticulum [ER], ribosome, proteasome, polysome, and endosome) (for more details, see references 177, 300, and 466). Notably, replication pathways of DNA viruses (HCMV, HBV, HPV, HSV, and VZV), RNA viruses (HCV, RSV, and influenza virus), and retroviruses (HIV) diverge after entering host cells. The RNA viruses replicate in the cytoplasm, but DNA viruses and retroviruses further intrude into the nucleus for their DNA synthesis. Note that drug group XIII is not displayed because drugs in this group act mainly as immunoregulatory or antimitotic agents, and they do not directly target viral proteins. Shapes and sizes of proteins and cellular components are not to scale.

TABLE 3 Summary of forthcoming antiviral treatments in phase 3 trials

Antiviral drug	Viral infection	% efficacy[a]	Mechanism(s) of action	Study progress[b]
Sofosbuvir + velpatasvir	HCV genotypes 1–6	97.4	Inhibit activities of HCV NS5B polymerase and NS5A, respectively	Phase 3, completed
Daclatasvir + asunaprevir	HCV genotype 1	86.4	Daclatasvir, asunaprevir, and beclabuvir inhibit activities of NS5A, NS3/4A protease, and NS5B, respectively	Phase 4, ongoing
Daclatasvir + asunaprevir + beclabuvir	HCV genotype 1	91.5		Phase 3, ongoing
FV100	VZV	87.6	Inhibits activity of the VZV DNA polymerase[c]	Phase 3, ongoing
Letermovir	HCMV	71	Targets the pUL56 subunit of the HCMV terminase complex to block viral DNA processing and/or packaging[d]	Phase 3, ongoing

[a] For HCV inhibitors, drug efficacy is measured by the SVR12 (see the text). For the VZV inhibitor FV100, drug efficacy is measured by the incidence of patients without postherpetic neuralgia after treatment at 90 days. For the HCMV inhibitor letermovir, drug efficacy is measured by the incidence of successful prophylaxis after treatment at 12 weeks (392).
[b] Clinical data were extracted from ClinicalTrials.gov (see https://www.clinicaltrials.gov/) in April 2016.
[c] See reference 385.
[d] See references 389 and 390.

tent humans have been reported, including pneumonia, cellulitis, neuralgia, encephalitis, myelitis, cranial nerve palsies, or peripheral nerve palsies (83). It has been estimated that 30% of humans have been infected with herpes zoster over their lifetime (83), and the seroprevalence of immunoglobulin G (IgG) antibody to varicella-zoster virus is >86% in children and adults (84). In the United States, VZV infections give rise to 1 million cases or more each year (83, 85).

The nine human viruses described above have caused devastating infectious diseases that afflict millions of humans worldwide (Table 1), therefore calling for the urgent development of effective antiviral drugs. The following sections focus on the molecular and therapeutic aspects of approved antiviral drugs against these 9 human viruses.

5-SUBSTITUTED 2′-DEOXYURIDINE ANALOGUES

Three antiviral drugs (idoxuridine, trifluridine, and brivudine [BVDU]) have been approved in the drug group of 5-substituted 2′-deoxyuridine analogues (Table 2). Historically, the era of antiviral chemotherapies started in 1959 with the description of idoxuridine (5-iodo-2′-deoxyuridine) by William H. Prusoff (86). Although idoxuridine was originally described as a potential antitumor agent, it would later become the first antiviral drug to be used (and it still is) clinically for the topical treatment of herpetic eye infection (i.e., keratitis due to HSV). Herrmann was the first to report the antiviral activity of idoxuridine against HSV and vaccinia virus in 1961 (87). Herrmann was also the first to propose the use of idoxuridine against HSV keratitis in rabbits (88) and humans (89). Thereafter, Kaufman and Heidelberger described the effectiveness of trifluridine (5-trifluoromethyl-2′-deoxythymidine) against HSV infections (90). Idoxuridine and trifluridine are now used for the topical treatment (such as in eye drops or eye ointment) of HSV epithelial keratitis (91).

Idoxuridine and trifluridine alone cannot be considered specific antiviral agents, for they must be phosphorylated by cellular kinases to either the 5′-triphosphate (TP) form (i.e., idoxuridine) or the 5′-monophosphate form (i.e., trifluridine), both of which actively inhibit viral and cellular DNA synthesis (3) (Fig. 5). As an analogue of the nucleoside thymidine, brivudine [(*E*)-5-(2-bromovinyl)-2′-deoxyuridine] is highly specific in its activity against HSV-1 and VZV (92, 93). Moreover, brivudine is superior to either idoxuridine, trifluridine, or acyclovir in cell culture experiments (94). To achieve its inhibitory activity, brivudine is specifically phosphorylated by the thymidine kinases of HSV-1 and VZV, which convert brivudine to its 5′-mono- and 5′-diphosphate forms. The cellular nucleoside 5′-diphosphate kinases further phosphorylate the 5′-mono- and 5′-diphosphates of brivudine into the 5′-triphosphate of brivudine, which targets the viral DNA polymerase for the inhibition of viral DNA synthesis (92).

BVDU has been approved in many countries all over the world (except for the United States and the United Kingdom) for the oral treatment of VZV infections, i.e., herpes zoster (shingles), for which it is prescribed at a dosage of 125 mg per day (for 7 days). Moreover, brivudine is used as eye drops for the treatment of HSV-1 epithelial keratitis. A systematic review, which collected data from 106 comparative treatment trials enrolling 5,872 cases with HSV infections, demonstrated that treatment with brivudine at 14 days was at least as effective as acyclovir and ganciclovir, two acyclic guanosine analogues (91). Ophthalmic preparations of brivudine, trifluridine, acyclovir, and ganciclovir are equally effective, allowing ~90% of treated eyes to recover within 2 weeks (91). Unlike idoxuridine and trifluridine, which cause high toxicity, brivudine has a favorable safety profile and can be administered systemically to treat HSV-1 and VZV (93). Moreover, brivudine might be used to treat Epstein-Barr virus (EBV) encephalitis (95, 96), but this new application has yet to be proven in clinical trials.

NUCLEOSIDE ANALOGUES

The drug group of nucleoside analogues includes three FDA-approved drugs: vidarabine, entecavir (ETV), and telbivudine (Table 2). Historically, arabinosyl nucleoside analogues were first isolated from sponges (97). Before Schabel (98) documented its antiviral potential, arabinosyladenine was first considered to be a potential anticancer agent (99). With high potency against HSV and VZV (e.g., herpes zoster) infections, vidarabine, which targets viral DNA polymerases (Fig. 5), was the first of the FDA-approved nucleoside analogues to be administered systemically in clinics (100, 101). However, vidarabine is barely soluble in aqueous medium, and it is rapidly deaminated by adenosine deaminases to its inosine counterpart (ara-Hx [arabinosylhypoxanthine]). Since

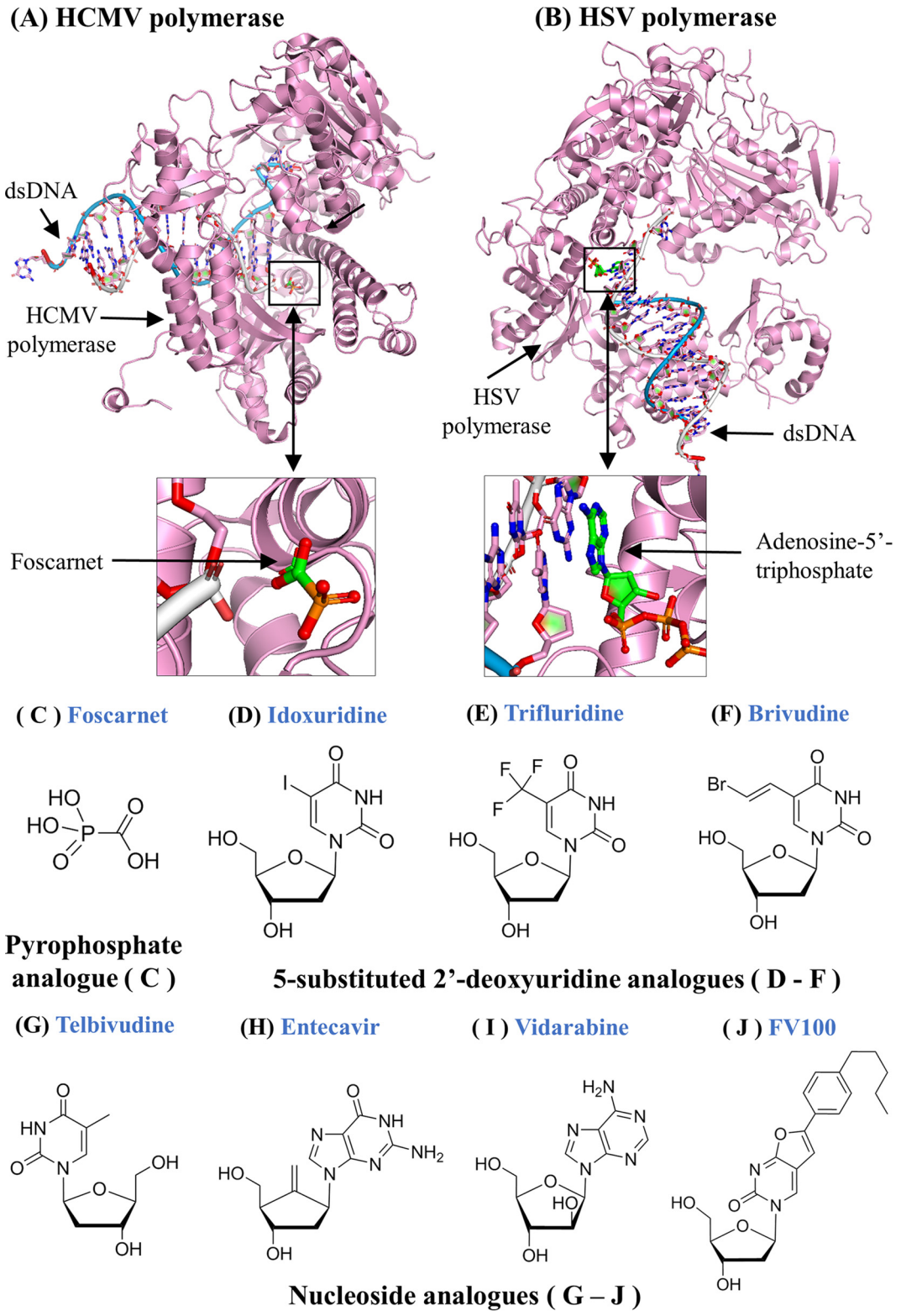

FIG 5 HCMV and HSV-1 DNA polymerase structures and chemical formulas of pyrophosphate analogues, 5-substituted 2′-deoxyuridine analogues, and nucleoside analogues. (A) Tertiary structures of HCMV DNA polymerase in complex with dsDNA and foscarnet (PDB accession number 3KD5). HCMV DNA polymerase is shown in pink. The dsDNA is placed in the center, where foscarnet inhibits DNA synthesis at the active site of HCMV DNA polymerase. Structural movies that demonstrate drug binding are available online (see http://www.virusface.com/). PyMOL V1.7 visualization software (http://www.pymol.org/) was used. (B) Tertiary structures of HSV-1 DNA polymerase complexed with dsDNA and ATP (PDB accession numbers 2GV9 and 4M3R). HSV-1 DNA polymerase is shown in pink. ATP near the catalytic site is displayed in the drug-binding pocket. The triphosphate form of approved antiviral inhibitors (e.g., vidarabine triphosphate) can compete with dATP to inhibit the replication activity of HSV DNA polymerase. (C) Chemical formula of foscarnet in the group of pyrophosphate analogues. (D to F) Chemical formulas of idoxuridine, trifluridine, and brivudine in the group of 5-substituted 2′-deoxyuridine analogues. (G to J) Chemical formulas of telbivudine, entecavir, vidarabine, and FV100 in the group of nucleoside analogues. Note that FV100 is an experimental inhibitor in phase 3 clinical trials.

June 2001, vidarabine has been discontinued in the United States, probably for commercial reasons (102).

For the treatment of HBV infections, the following compounds have been licensed: (pegylated) interferons, lamivudine, entecavir, telbivudine, adefovir dipivoxil, and tenofovir disoproxil fumarate (TDF) (Table 2). Lamivudine and TDF have also been licensed for the treatment of HIV infections and are further discussed below. Two nucleoside analogues, entecavir and telbivudine, are exclusively used for the treatment of HBV infections (Fig. 5). In patients with either HBeAg-positive ($HBeAg^+$) chronic hepatitis B (103) or HBeAg-negative chronic hepatitis B (104), the rates of histological, virological, and biochemical improvements were significantly higher with entecavir than with lamivudine. More importantly, long-term monitoring of nucleoside-naive patients receiving 5 years of entecavir therapy showed a low rate of HBV resistance to entecavir (105). However, it came as a surprise when entecavir was reported to inhibit HIV-1 infections with only modest activity (106, 107), because this might generate HIV-1 resistance to entecavir in patients coinfected with HIV-1 and HBV. The "take-home" message was not to use entecavir in such patients (107).

Several phase 2 or 3 clinical trials compared the potencies and safeties of telbivudine versus lamivudine, and their findings suggested that telbivudine offered greater HBV DNA suppression with less resistance than did lamivudine (108–110). For instance, a randomized, double-blind, phase 3 trial that enrolled 1,367 patients infected with chronic HBV suggested that telbivudine was superior to lamivudine in terms of higher rates of undetectable viremia and less resistance (111). For treatment of $HBeAg^+$ mothers during late pregnancy, telbivudine was well tolerated, with no severe side effects in telbivudine-treated mothers or their infants (112). Although entecavir is superior to telbivudine in safety, both telbivudine and entecavir offer similar drug efficacies in terms of the cumulative rates of undetectable HBV DNA and alanine aminotransferase levels (113). For first-line therapy of HBV infections, the use of entecavir is strongly recommended, especially in children aged 2 to 12 years (114). Nevertheless, telbivudine, lamivudine, and adefovir dipivoxil are not recommended because they have a low barrier to resistance (114).

Overall, orally administered nucleos(t)ide analogues, with their safety, easy use, and low drug resistance rates, are preferable for HBV treatments, but the high costs of these drugs remain a great concern in resource-limited areas. Therefore, lamivudine is commonly used in first-line therapy regardless of its high rate of drug resistance (115).

PYROPHOSPHATE ANALOGUES

Trisodium phosphonoformate, known as foscarnet (Fig. 5), was discovered as a new antiviral compound in 1978 (116). Although it is the only approved inhibitor in this drug group, foscarnet was not the first pyrophosphate analogue, as it had been preceded by phosphonoacetic acid (117). The novelty of foscarnet and phosphonoacetic acid depends on the fact that these compounds are unlike other classical antiviral agents (i.e., BVDU and acyclovir), because they do not have to be phosphorylated (i.e., metabolized to their active metabolite) before their binding to drug targets (i.e., viral DNA polymerases) (118). Therefore, foscarnet could be selected directly at the enzyme level (116).

In a comprehensive review, Bo Öberg (119) ascertained that foscarnet achieved its broad-spectrum activity against HSV-1, HSV-2, VZV, HCMV, EBV, HIV, and HBV by targeting viral DNA polymerases (Fig. 5). However, foscarnet neither showed inhibitory activities against viral RNA polymerases nor inhibited the replication of RNA viruses (except for retroviruses) (119). Despite its inhibitory activity, specifically confined to DNA viruses and retroviruses, foscarnet acts in a unique fashion because it binds directly, as a pyrophosphate analogue, to viral DNA polymerases (Fig. 5). Foscarnet is unlike nucleos(t)ide analogues that must be phosphorylated to their triphosphate (nucleoside) or diphosphate (nucleotide) forms before their binding to viral DNA polymerase (Fig. 5).

Foscarnet is used exclusively in the treatment of HCMVs or HSVs that have become resistant to the classical nucleoside analogues such as acyclovir. As shown in some case reports, the effectiveness of foscarnet has been demonstrated in the treatment of infection by thymidine kinase-deficient HSV strains with resistance to acyclovir (120–122). Clinical evidence also suggests that foscarnet-based treatments efficiently improve the clinical outcomes of HIV-infected patients with HSV infections (123). For the treatment of HCMV infections, foscarnet-based regimens may eradicate viremia rapidly, yet their efficacy is limited because of a high level of toxicity in the long term (124). Common side effects with foscarnet are nausea, diarrhea, vomiting, headache, renal impairment, or ionized hypocalcemia (125, 126).

In addition to its antiviral activity against HCMV and HSV infections, foscarnet is effective against human herpesvirus 6 (HHV-6), a widespread betaherpesvirus genetically related to HCMV (127). Despite its promising activity against HHV-6, foscarnet has not been approved to treat HHV-6. Therefore, further clinical trials will still be required to prove this potential in the future.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Soon after its discovery as an anti-HIV agent in 1985 (128), zidovudine (AZT [azidothymidine]) was licensed for clinical use in 1987. Zidovudine is not only the first drug approved for HIV treatment but also the first drug in the group of NRTIs, which target HIV reverse transcriptase to interfere with viral reverse transcription (Fig. 6). Inspired by the success of zidovudine, 6 drugs in the group of NRTIs (Fig. 6) were subsequently approved to treat HIV or HBV infections: (i) didanosine (ddI [2′,3′-dideoxyinosine]) (129), (ii) zalcitabine (ddC [2′,3′-dideoxycytidine]) (129), (iii) stavudine (d4T [2′,3′-didehydro-3′-deoxythymidine]) (130–132), (iv) lamivudine (3TC [2′,3′-dideoxy-3′-thiacytidine]) (133), (v) abacavir (ABC) [(1*S*,4*R*)-4-(2-amino-6-(cyclopropylamino)-9H-purin-9-yl)-2-cyclopentene-1-methanol] (134), and (vi) emtricitabine [(−)FTC (2′,3′-dideoxy-5-fluoro-3′-thiacytidine), where "(−)" indicates the L-enantiomeric form] (135).

All NRTI compounds are known as 2′,3′-dideoxynucleoside analogues, with similar mechanisms of drug action. After their phosphorylation to the 5′-TP, NRTIs act as chain terminators, a mechanism of drug action originally shown for AZT (136), with (i) AZT-TP in competition with dTTP (137), (ii) ddATP (formed from ddI) in competition with dATP, (iii) ddCTP (formed from ddC) in competition with dCTP, (iv) d4T-TP (formed from d4T) in competition with dTTP, (v) 3TC-TP (formed from 3TC) in competition with dCTP, (vi) carbovir-TP (formed from ABC) in competition with dGTP, and (vii) (−)FTC-TP [formed from (−)FTC] in competition with dCTP (4) (Fig. 6).

NRTIs alone are not administered in HIV treatments because

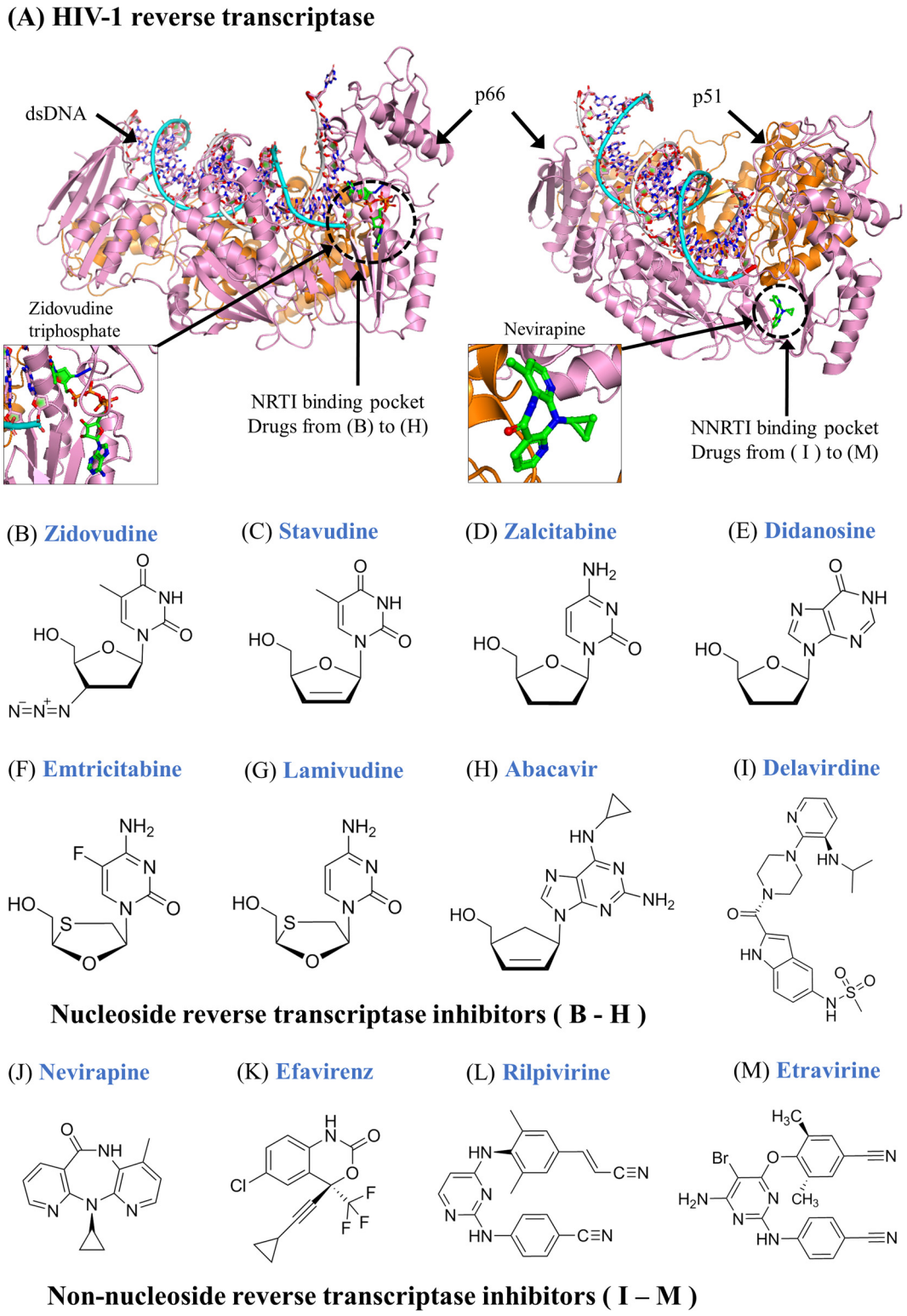

FIG 6 Tertiary structures of HIV-1 reverse transcriptase and chemical formulas of NRTIs and NNRTIs. (A) HIV-1 RT complexed with dsDNA and zidovudine triphosphate (left) (PDB accession number 3V4I) and nevirapine (right) (PDB accession number 4PUO). Two subunits of the HIV-1 RT heterodimer are shown in pink and orange, respectively. Zidovudine triphosphate targets the drug-binding pocket of NRTIs, known as the catalytic site, to inhibit the activity of HIV-1 RT during DNA synthesis. Nevirapine targets the drug-binding pocket of NNRTIs, known as the allosteric site, to block the activity of HIV-1 RT during DNA synthesis (see structural movies at http://www.virusface.com/). (B to H) Chemical formulas of zidovudine, stavudine, zalcitabine, emtricitabine, didanosine, lamivudine, and abacavir in the group of NRTIs. (I to M) Chemical formulas of delavirdine, nevirapine, efavirenz, rilpivirine, and etravirine in the group of NNRTIs.

NRTIs usually have a low genetic barrier to the development of drug resistance mutations, which have been characterized by the International Antiviral Society-USA (IAS-USA) panel (138) and the HIV drug resistance database (http://hivdb.stanford.edu/). NRTIs are commonly administered with other drugs in highly active antiretroviral therapy (HAART) to target multiple stages of the HIV life cycle (139, 140). In particular, both lamivudine and emtricitabine are backbones in 9 approved combination drugs (Table 2): (i) lamivudine plus zidovudine (Combivir); (ii) lamivudine plus zidovudine and ABC (Trizivir); (iii) lamivudine plus the integrase inhibitor dolutegravir (Dutrebis); (iv) lamivudine plus dolutegravir and abacavir (Triumeq); (iii) emtricitabine plus TDF (Truvada); (iv) emtricitabine plus TDF and efavirenz (Atripla); (v) emtricitabine plus TDF and the NNRTI rilpivirine (Complera or Eviplera); (vi) emtricitabine plus TDF, the integrase inhibitor elvitegravir, and cobicistat (Stribild); (vii) emtricitabine plus tenofovir alafenamide (TAF), elvitegravir, and cobicistat (Genvoya); (viii) emtricitabine plus TAF and rilpivirine (Odefsey); and (ix) emtricitabine plus TAF (Descovy). Although the pharmacological equivalence and clinical interchangeability of lamivudine and emtricitabine remain debated (141, 142), both drugs are key components of approved combination drugs.

In clinical practice, the most common side effects with NRTIs are reversible peripheral neuropathy, nausea, headache, rash, anemia, leukopenia, pancreatitis, gout, or hypersensitivity (143). It is also worth mentioning that because of its neurotoxicity, the FDA-approved agent zalcitabine has been discontinued since December 2006. As of today, NRTI drugs, patented mostly before 2003, are over their expiration dates for patents (144). Patent expiration thus stimulates broad marketing worldwide, making NRTIs popular first-line agents against HIV infections in resource-limited areas.

NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Discovered in the late 1980s, the group of NNRTIs includes five approved anti-HIV drugs: nevirapine, delavirdine, efavirenz, etravirine, and rilpivirine (Table 2). Historically, NNRTIs originated from two classes of compounds discovered independently from each other: 1-[(2-hydroxy-ethoxy)methyl]-6-phenylthiothymine (HEPT) analogues (145, 146) and tetrahydro-imidazo[4,5,1-jk][1,4]-benzodiazepine-2(1H)-one and -thione (TIBO) analogues (147). To inhibit viral replication, HEPT and TIBO derivatives target HIV-1 reverse transcriptase (148–150). Emivirine (MKC-442), derived from the HEPT derivatives (151), had reached phase 3 clinical trials before its further development was stopped (152). TIBO derivatives led through a highly meandrous route to the identification of diarylpyrimidine (DAPY) derivatives (153), including dapivirine, etravirine, and rilpivirine (154). Approved by the FDA, etravirine (Intelence) and rilpivirine (Edurant), accompanied by three other NNRTIs (delavirdine, efavirenz, and nevirapine), are now on the market. Delavirdine is currently rarely used due to its high toxicity, relatively low potency, and complex drug interactions (155).

Unlike NRTIs, NNRTIs do not need any metabolic processing to inhibit HIV reverse transcription (Fig. 6). Instead, they serve as noncompetitive inhibitors that target the allosteric site of HIV-1 RT, situated a short distance (~15 Å) from the RT catalytic site (156–158). This binding induces conformation changes to impair the catalytic activity of HIV-1 RT, thus interrupting viral replication (159). Importantly, NNRTIs act specifically against HIV-1, whereas HIV-2 is naturally resistant to all NNRTIs due to its structural properties (160). When RT structures of HIV-1 and HIV-2 were compared, differences were found at both conserved and nonconserved positions (K101, V106, E138, Y181, Y188, and G190) in the drug-binding pocket of NNRTIs (161). In addition to the above-mentioned positions, drug resistance mutations at other RT positions (V90, A98, L100, K103, V108, V179, H221, P225, F227, and M230) may also cause treatment failure of NNRTIs (138).

In clinical practice, NNRTIs are widely used as first-line agents. They can be combined with tenofovir disoproxil fumarate, (−)FTC, and rilpivirine to afford a once-daily pill, Complera (United States) or Eviplera (European Union), for all-inclusive treatments of HIV infections (153). The most common side effects with NNRTIs are rash, central nervous system toxicity, or elevation of liver enzyme levels (143). Promising NNRTIs such as doravirine (MK-1439) (162–164) and diarylpyrimidine (165) are under investigation in clinical trials.

PROTEASE INHIBITORS

In the group of protease inhibitors (PIs), 12 HIV protease compounds and 7 HCV NS3/4A protease compounds have been approved for clinical use (Table 2). HIV and HCV protease inhibitors are described below.

HIV Protease Inhibitors

Historically, HIV-1 protease (Fig. 7) was first proposed as a potential target for AIDS therapy by Kramer et al. (166), when they showed that a frameshift mutation in the protease region of the *pol* gene prevented protease-mediated cleavage of *gag* precursor proteins (167). The transition state mimetic concept later inspired Roberts and coworkers to describe the rational design of peptide-based protease inhibitors (167). In 1995, saquinavir was approved as the first protease inhibitor, marking the beginning of an era for this new class of anti-HIV inhibitors. In fact, not only saquinavir but also 9 out of the 10 approved HIV protease inhibitors are based on the same principle, in which the hydroxyethylene bond acts as the peptidomimetic scaffold, including saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, and darunavir (Fig. 7). The only exception is tipranavir, which is built on the coumarin scaffold (168). When protease inhibitors compete with natural substrates of HIV protease as the peptidomimetic scaffold (169), amino acid variations near this scaffold and within the cleavage sites of protease substrates (i.e., Gag and Gag-Pol) may have been selected during virus evolution to cause resistance to HIV protease drugs (170, 171). Except for the discontinued agent amprenavir (Agenerase), which is superseded by fosamprenavir, other protease inhibitors are still widely used for HIV infections. Common side effects with PIs are nephrolithiasis, hypertension, rash, diarrhea, elevation of liver enzyme levels, ingrown toenails, benign hyperbilirubinemia, and gastrointestinal upset (143).

HIV protease inhibitors are key components of HAART for patients infected with HIV-1 and/or HIV-2. However, primary and secondary resistance mutations in HIV protease remain a concern for administering PIs to patients harboring drug-resistant viruses (138, 169, 172). Because of the innate differences between HIV-1 and HIV-2 proteases (173), different PI-based treatments have been recommended for HIV-1 and HIV-2 infections to take resistance-associated mutation patterns into account

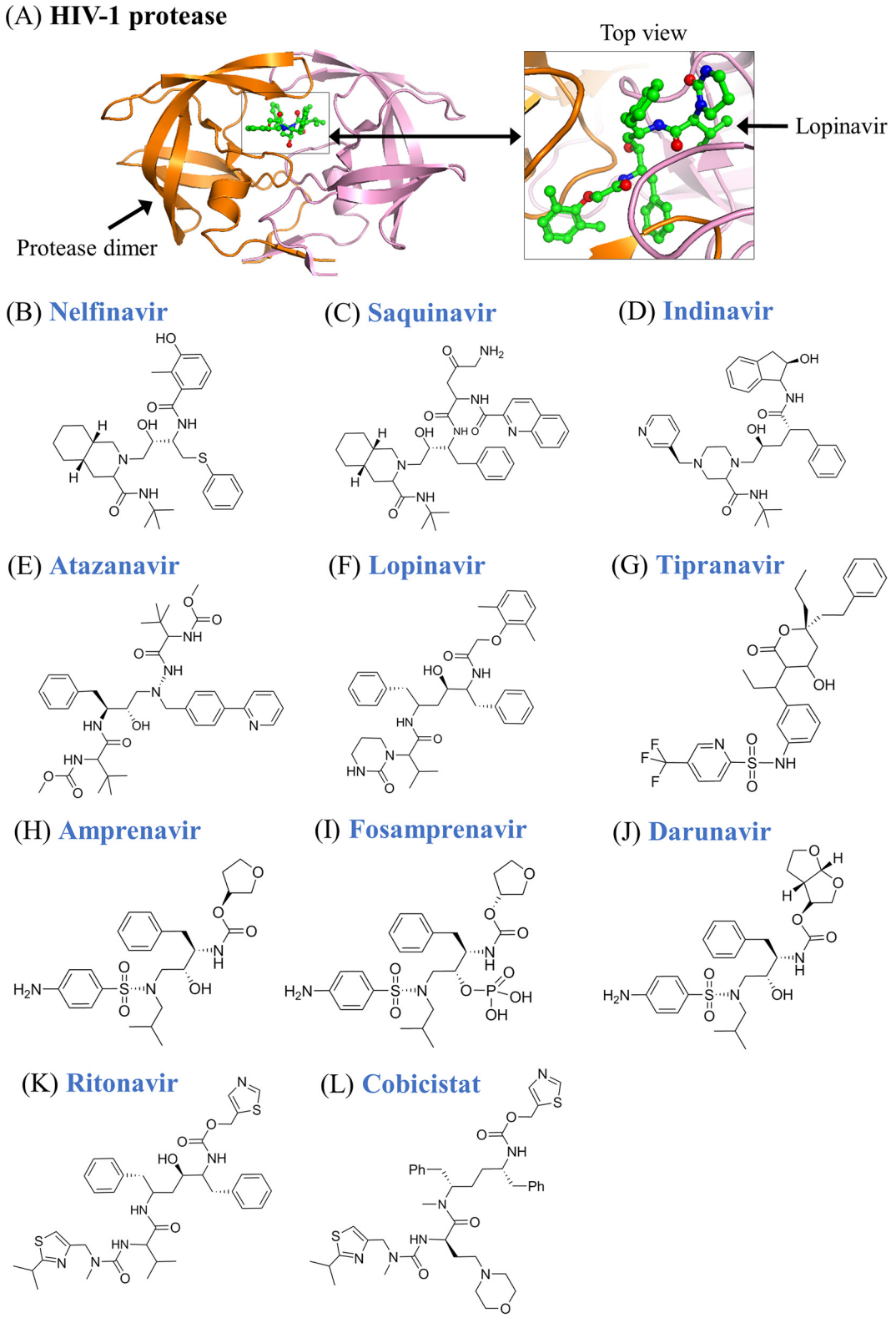

FIG 7 Tertiary structures of HIV-1 protease and chemical formulas of HIV protease inhibitors. (A) HIV-1 protease dimer complexed with lopinavir (PDB accession number 2Q5K). The side view (left) and top view (right) of structures are presented. (B to K) Chemical formulas of nelfinavir, saquinavir, indinavir, atazanavir, lopinavir, ritonavir, fosamprenavir, amprenavir, darunavir, and tipranavir in the group of protease inhibitors. (L) Chemical formula of cobicistat. Cobicistat is a pharmacoenhancer used with HIV protease inhibitors, but cobicistat alone shows no antiviral activity.

(140). In contrast to the wide application of PIs approved for HIV-1 infection, current U.S. and European treatment guidelines recommend the use of lopinavir/ritonavir (LPV/r), saquinavir/ritonavir (SQV/r), or darunavir/ritonavir (DRV/r) for patients infected with HIV-2, because many polymorphisms in HIV-2 cause natural resistance to PIs such as tipranavir and fosamprenavir (140, 174, 175). Note that ritonavir is a popular booster that improves the bioavailability and half-lives of other PIs, so a low dose of ritonavir is commonly coadministered with other PIs (e.g., LPV/r) (169). In a similar fashion, cobicistat has been approved as a pharmacoenhancer of PIs. Although it has no antiviral activity, cobicistat inhibits intestinal transport proteins (cytochrome P450 enzymes of the CYP3A family) and increases the overall absorption of PIs (176). Approved by the FDA, cobicistat is now coadministered with the PIs darunavir (Prezcobix) and atazanavir (Evotaz) as well as other anti-HIV drugs (Stribild and Genvoya), which are elucidated below.

HCV NS3/4A Protease Inhibitors

Despite fundamental differences in their structures and modes of replication, HIV and HCV share some similarities because both viruses cleave precursor proteins by viral proteases (aspartic protease for HIV versus serine protease for HCV) (Fig. 8), which could serve as ideal targets for the design of protease inhibitors (177). Of many protease inhibitor candidates, the following seven compounds that efficiently inhibit the activity of HCV NS3/4A protease are momentarily on the market (Fig. 8): asunaprevir, boceprevir, paritaprevir, simeprevir, telaprevir, vaniprevir, and grazoprevir (178–180). Among them, boceprevir (Victrelis) and telaprevir (Incivek) were discontinued for commercial reasons. To treat patients with HCV genotype 1 infection, combination drugs of asunaprevir plus daclatasvir and vaniprevir plus pegylated interferon alfa 2b (PegIFNα-2b) plus ribavirin have been approved in Japan (181).

All approved NS3/4A protease inhibitors are used for treatment of infection by HCV genotype 1, the most prevalent genotype in HCV-infected populations (182). Compared to two discontinued drugs, telaprevir and boceprevir, simeprevir has better response rates and drug interaction profiles, although it is more expensive. As a potent inhibitor approved by the FDA, paritaprevir is now used in combination with ombitasvir plus ritonavir (Viekira Pak) or ombitasvir plus dasabuvir plus ritonavir (Technivie) to treat HCV genotype 1 and 4 infections, respectively (Table 2). Approved by the FDA in January 2016, a combination drug of grazoprevir plus elbasvir (Zepatier) is now applied to treat HCV genotype 1 or 4 infection (Table 2). In addition to the approved drugs mentioned above, many experimental NS3/4A protease inhibitors (danoprevir, faldaprevir, vedroprevir, sovaprevir, deldeprevir, and narlaprevir) have been (or still are) under clinical development (178, 179). Forthcoming HCV protease inhibitors may have a reduced potential for drug-drug interactions, thus improving their use in the treatment of HCV infections (183).

INTEGRASE INHIBITORS

Since the first HIV integrase inhibitor was approved in 2007, three FDA-approved integrase inhibitors (raltegravir, dolutegravir, and elvitegravir) have been frequently used in HAART. Integrase inhibitors are described below.

Raltegravir

During virus integration, viral integrases insert proviral DNA into host genomes through a multistep process. As an essential step, the strand transfer reaction covalently links the proviral DNA 3′ ends to the cellular (target) DNA, and this strand transfer can be inhibited by the so-called diketo acid inhibitors (184). These diketo acids (i.e., L-870812) could actively suppress the replication of simian-human immunodeficiency virus (SHIV) in rhesus macaques (185). This led to the discovery of raltegravir (MK-0518) as the "first in class" among the integrase inhibitors, which target the catalytic site of HIV integrase to prevent virus integration (Fig. 9). Raltegravir was later added to an optimized background regimen (OBR) (186), offering better virus suppression than the OBR alone (187). The use of raltegravir was effective, particularly for the treatment of HIV-infected patients with high HIV-1 RNA levels, low CD4 cell counts, and low genotypic or phenotypic sensitivity scores (188). Raltegravir could be combined with two nucleos(t)ide analogues or with ritonavir-boosted lopinavir (189). Since there is no raltegravir-based combination approved by the FDA, the effectiveness of such combination drugs has yet to be elucidated in clinical trials.

Elvitegravir

In 2006, Sato and coworkers first showed that the 4-quinolone-3-carboxylic acids could be an alternative scaffold to diketo acids, leading to the discovery of elvitegravir (GS-9137), which efficiently inhibited the DNA strand transfer reaction of HIV-1 integrase (190). Subsequent *in vitro* studies indicated that elvitegravir inhibited not only strains of various HIV-1 subtypes but also a broad spectrum of viruses such as HIV-2, murine leukemia virus, and simian immunodeficiency virus (SIV) (191, 192). Akin to raltegravir, elvitegravir can be used in combination with nucleos(t)ide analogues. Stribild, which contains elvitegravir, cobicistat, (−)FTC, and TDF (193), was approved as the first once-daily four-drug ("quad") pill in August 2012. Stribild causes minimal adverse effects but efficient virus suppression comparable to those for other HIV combination drugs (e.g., Atripla) (194, 195). Approved in November 2015, Genvoya is another combination drug that contains elvitegravir plus cobicistat, (−)FTC, and tenofovir alafenamide.

When the efficacy and safety of elvitegravir was compared with those of raltegravir, a phase 3 clinical trial suggested that both drugs are comparable, but elvitegravir might improve patients' adherence because elvitegravir requires only once-daily dosing, compared with twice-daily dosing for raltegravir (196). Elvitegravir is usually well tolerated, while the most common side effects are diarrhea and nausea (197). It is worth mentioning that elvitegravir should not be used to treat raltegravir-resistant HIV infections, because elvitegravir shares similar drug resistance mutations with raltegravir (198).

Dolutegravir

Approved by the FDA in August 2013, dolutegravir is the third integrase inhibitor on the market. Even though dolutegravir and raltegravir share similar efficacies and safety profiles (199), dolutegravir exhibits a higher genetic barrier to drug resistance development (200). Moreover, once-daily dolutegravir, in combination with up to two other antiretroviral drugs, provides a better virologic response than twice-daily raltegravir in antiretroviral-experienced patients (201). In a phase 3b clinical trial called

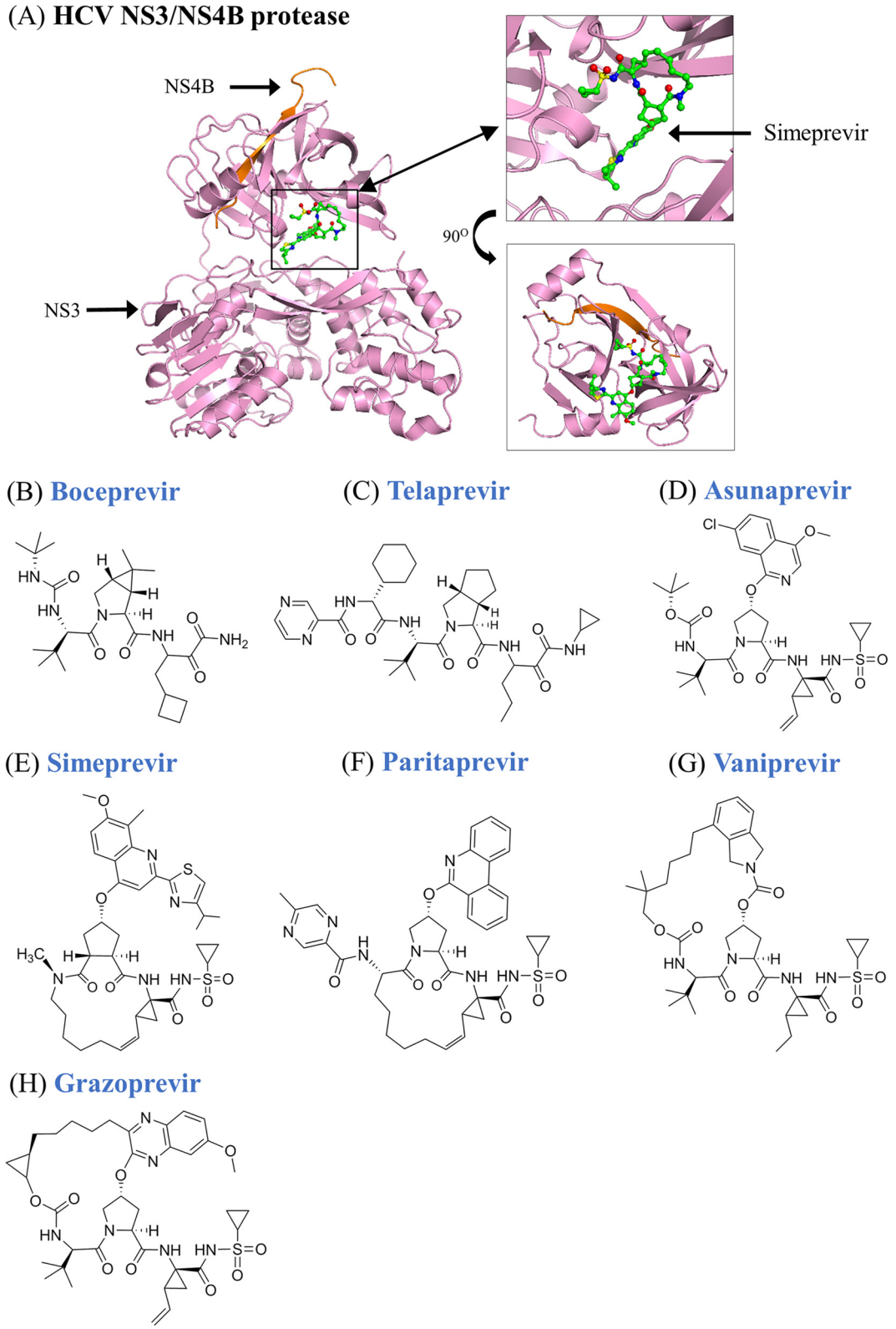

FIG 8 Tertiary structures of HCV NS3/NS4B protease and chemical formulas of HCV protease inhibitors. (A) HCV NS3/NS4B protease in complex with simeprevir (PDB accession numbers 3KEE and 4B76). HCV NS3 and NS4B proteins are shown in pink and orange, respectively. (B to H) Chemical formulas of boceprevir, telaprevir, asunaprevir, simeprevir, paritaprevir, vaniprevir, and grazoprevir in the group of HCV protease inhibitors.

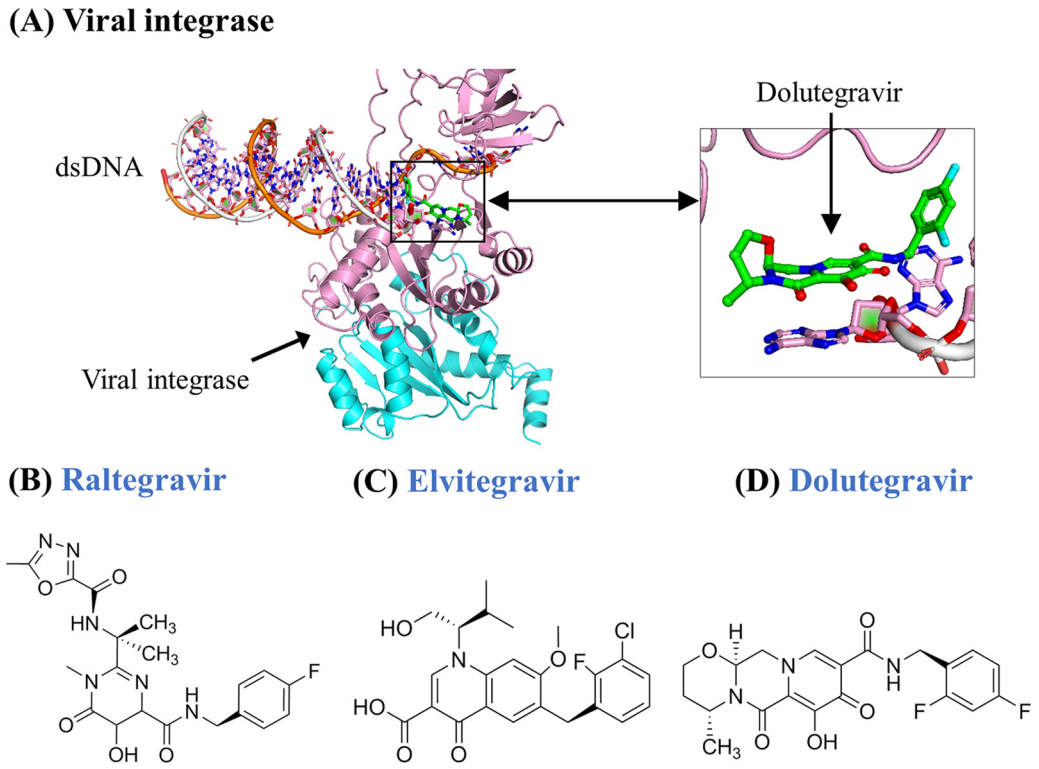

FIG 9 Tertiary structures of viral integrase and chemical formulas of HIV integrase inhibitors. (A) Viral integrase of prototype foamy virus in complex with dsDNA and dolutegravir (PDB accession number 3S3N). A dimer structure of the viral integrase is shown in pink and cyan, respectively. Although the structure of HIV integrase in complex with its inhibitors is still lacking, approved antiviral inhibitors that target HIV and prototype foamy virus integrase are believed to share similar mechanisms (477). (B to D) Chemical formulas of raltegravir, elvitegravir, and dolutegravir in the group of HIV integrase inhibitors.

FLAMINGO, once-daily dolutegravir was superior to once-daily darunavir plus ritonavir for the treatment of antiretroviral-naive patients infected with HIV-1 (202, 203). Due to its prominent antiviral activity, dolutegravir is now used in two fixed-dose combinations: dolutegravir plus abacavir plus lamivudine (Triumeq) (one tablet, once daily) and dolutegravir plus lamivudine (Dutrebis) (one tablet, twice daily) (Table 2).

In first-line therapy, integrase inhibitors are superior to NRTIs, NNRTIs, and protease inhibitors (200). Even though integrase inhibitors have a high genetic barrier to resistance (200), drug resistance mutations (e.g., F121Y, Q148H/R, N155H, and R263K) have been observed for all three integrase inhibitors (138). The most common side effects with integrase inhibitors are nausea, diarrhea, hepatitis, or hypersensitivity (200). Attracted by their potent antiviral activities, forthcoming integrase inhibitors are under investigation in clinical trials. For instance, cabotegravir (GSK1265744 and GSK744) has been recognized as a long-acting inhibitor against the strand transfer reaction of HIV and SIV integrases (204–206). Recently, the potent anti-HIV activity of therapy with cabotegravir plus rilpivirine was shown in a randomized, phase 2b, dose-ranging trial (207), but more evidence is still required to support its clinical use. Overall, integrase inhibitors have offered good tolerability, a favorable safety profile, and an absence of significant drug interactions (200).

ENTRY INHIBITORS

In the drug group of entry inhibitors, there are 7 FDA-approved drugs, including one HSV drug (docosanol), two HIV drugs (enfuvirtide and maraviroc), two RSV antibody drugs (palivizumab and respiratory syncytial virus immune globulin, intravenous [RSV-IGIV]), and two VZV antibody drugs (varicella-zoster immunoglobulin [VariZIG] and varicella-zoster immune globulin [VZIG]) (Table 2). These entry inhibitors are described in the following sections.

Enfuvirtide and Maraviroc

Enfuvirtide (also known as T20), the first peptide inhibitor approved by the FDA, is a polypeptide (36 amino acids in length) homologous to the heptad repeat region of HIV-1 GP41 (208) (Fig. 10). To block the fusion of HIV-1 with the extracellular membrane of host cells, enfuvirtide mimics the helix in heptad repeat 2 (HR-2) to prevent the interaction between HR-1 and HR-2 (209, 210). Kilby et al. (211) showed the significant efficacy of enfuvirtide against HIV-1 replication in cell lines and human subjects. Approved by the FDA in March 2003, enfuvirtide is still the only anti-HIV drug that must be injected subcutaneously twice daily. It has been used for salvage therapies as part of combination regimens with other antiviral drugs (212, 213). Although enfuvirtide has high drug efficacy with minimal systemic toxicity, its long-term application is limited due to the subcutaneous administration and the high cost (214). The clinical use of enfuvirtide has therefore become obsolete given the wealth of the other 40 approved drugs against HIV infections by oral drug delivery.

Maraviroc is the first FDA-approved chemokine receptor antagonist or CCR5 inhibitor that targets the chemokine receptor CCR5 on the surface of $CD4^+$ cells and macrophages (215)

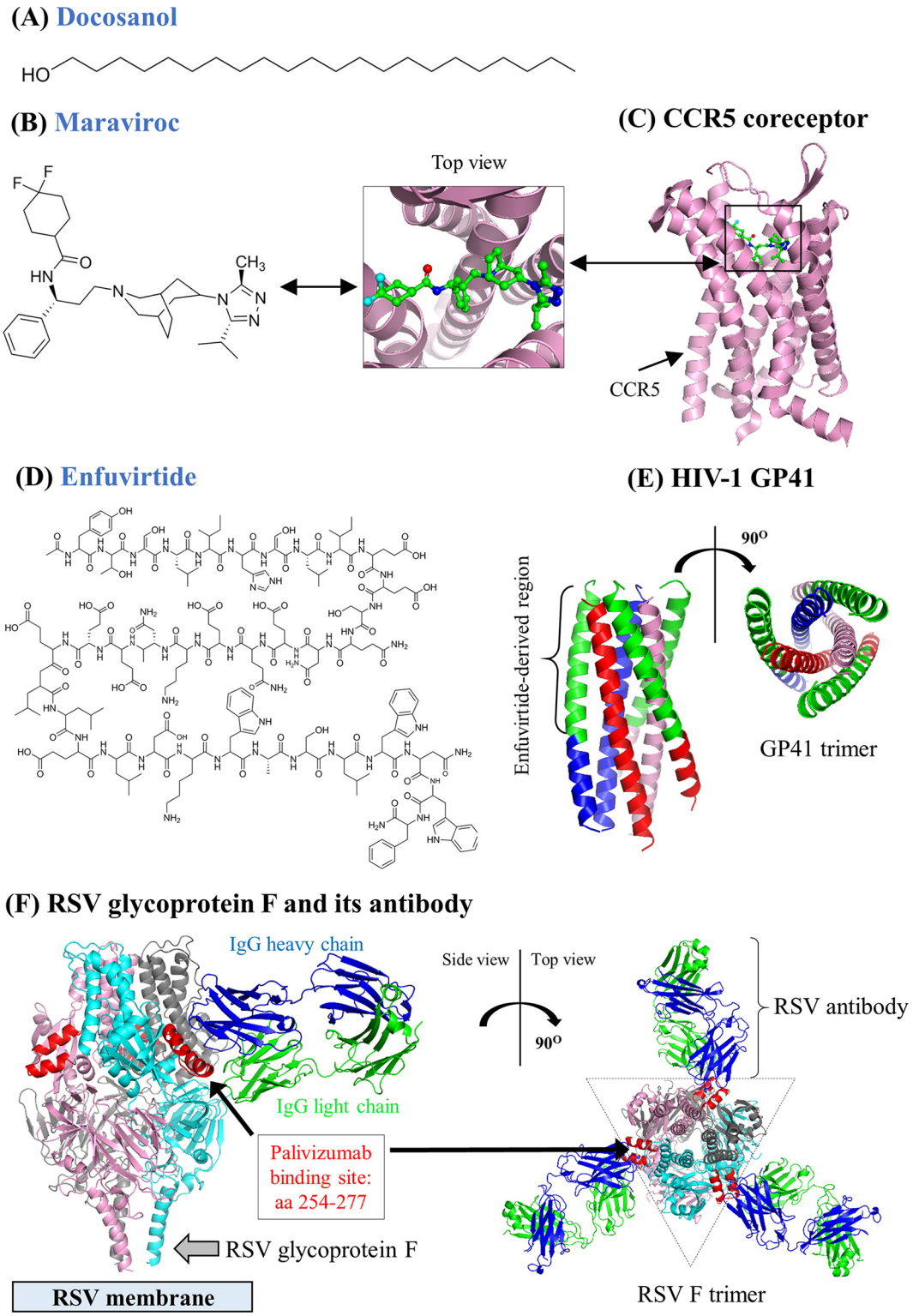

FIG 10 Chemical formulas of HIV entry inhibitors and tertiary structures of CCR5, HIV-1 GP41, and RSV glycoprotein F. (A) Chemical formula of docosanol. (B and C) Chemical formula of maraviroc and the CCR5 coreceptor in complex with maraviroc (PDB accession number 4MBS). The top and side views of the CCR5 structure are presented. (D and E) Chemical formula of enfuvirtide and tertiary structure of the HIV-1 GP41 trimer (PDB accession number 2X7R). Enfuvirtide is derived from the green region of HIV-1 GP41. The top and side views of the HIV-1 GP41 trimer are presented. Three units of the HIV-1 GP41 trimer are shown in blue, red, and pink, respectively. (F) Tertiary structure of the prefusion RSV glycoprotein F trimer in complex with the antibody motavizumab (PDB accession number 4ZYP). Motavizumab is an experimental monoclonal antibody derived from the FDA-approved drug palivizumab (478). The side views (left) and top views (right) of protein structures are presented. The heavy and light chains of motavizumab are shown in blue and green, respectively. The palivizumab-binding site (amino acid [aa] positions 254 to 277 [479]) is highlighted in red. Three units of the prefusion RSV F trimer are shown in pink, gray, and cyan, respectively.

(Fig. 10). Historically, Ed Berger and colleagues were the first to demonstrate the importance of the CC chemokine receptor CCR5 during HIV entry (216). Baba et al. (217) were the pioneers who described the first CCR5 antagonist, TAK-779, which, however, was not pursued due to its poor oral bioavailability. Likewise, TAK-220 and TAK-652, despite their oral bioavailability (218), were not developed further, nor were two CCR5 antagonists, aplaviroc and vicriviroc (219). Later, the principle of attacking CCR5 was proven to be a success when maraviroc showed promising antiviral activities in cell lines (220) and clinical trials (221, 222). It is worth mentioning that during early HIV infection, R5 viruses predominately use CCR5 for virus entry, whereas R4 viruses using CXCR4 usually occur at late stages of disease progression (223). For patients with R5 HIV-1 infections, maraviroc is a valuable treatment option (222, 224). However, maraviroc does not inhibit R4 viruses, and half of patients infected with R4 viruses fail maraviroc-based treatments (225). Therefore, it is possible that CCR5 antagonists would accelerate disease progression by the selection of viruses using CXCR4 (214, 215). Overall, the use of maraviroc requires the phenotypic identification of R5 viruses, and the coadministration of CCR5 and CXCR4 antagonists has yet to be a therapeutic challenge (214, 226).

Palivizumab and RSV-IGIV

RSV-IGIV, approved by the FDA in January 1996, is a sterile human immunoglobulin produced from adult plasma with high titers of neutralizing antibodies to RSV (227). These neutralizing antibodies can prevent RSV surface glycoproteins F and G from anchoring to host cells (227). Although RSV-IGIV may efficiently decrease the numbers of hospitalizations and hospital days attributable to RSV (228), the high cost and strict guidelines on its use remain a problematic issue (229). As a more cost-effective drug (230), palivizumab (Synagis) marked the discontinuation of RespiGam in 2004 (231). Approved by the FDA in June 1998, palivizumab is a humanized mouse immunoglobulin monoclonal antibody that directly targets a conserved epitope of the A antigenic site of the RSV fusion protein (232) (Fig. 10F). Therefore, palivizumab offers neutralizing and fusion-inhibitory activities against RSV infections (232). In clinical practice, palivizumab prophylaxis is recommended only for preterm infants with chronic lung diseases or congenital heart diseases, mostly in the first year of life for infants born within 12 months of the onset of the RSV season (232). Despite the promising outcomes from clinical trials (233, 234), systematic reviews suggest that the limited clinical and social benefits are insufficient to justify the high cost of palivizumab prophylaxis (232, 235, 236). Consequently, the clinical use of palivizumab prophylaxis is not popular in most cases.

VZIG and VariZIG

Historically, VZIG was discovered in 1969 when immunoglobulin concentrates were extracted from patients convalescing from VZV infections. Subsequent serological and clinical studies suggested that VZIG could decrease the risk of complications and reduce clinical illness in immunocompromised patients (237, 238). After its application for 2 decades, VZIG was discontinued in October 2004 and was later superseded by a better product, called VariZIG. Approved by the FDA in December 2012, VariZIG is a detergent-treated, sterile, lyophilized preparation of IgG purified from human plasma harboring high levels of anti-VZV antibodies. VariZIG offers passive immunization for immunocompromised patients to generate IgG antibodies against VZV infections (239). Licensed for postexposure prophylaxis of VZV infections, VariZIG is administered intramuscularly to high-risk patients who lack evidence of immunity to VZV and are ineligible for VZV vaccination (240). VariZIG must be administered to patients within 96 h of exposure to VZV, and the dosing of VariZIG depends on body weight. Common side effects with VariZIG are headache and pain at the injection site. Overall, VariZIG offers a cornerstone for VZV postexposure prophylaxis, while approved antiviral drugs such as acyclovir are also recommended to be used either alone or with immunoglobulin therapy (81).

Docosanol

Docosanol (*n*-docosanol; behenyl alcohol) is a 22-carbon, saturated, primary alcohol (Fig. 10) that inhibits a broad spectrum of lipid-enveloped viruses (e.g., HSV, RSV, HCMV, and VZV) based on *in vitro* experiments (241, 242). Clinical evidence suggests that 10% docosanol topical cream is safe and effective to reduce the healing time and duration of symptoms for the treatment of recurrent herpes labialis caused by HSV-1 or HSV-2 infections (241). Although its mechanism of drug action is still debated (243), docosanol is believed to prevent virus entry by interfering with the interaction between epithelial cell membrane receptors and HSV envelope proteins (242, 244). Approved by the FDA in July 2000, docosanol remains the only over-the-counter medication in clinical use for cold sores and fever blisters.

ACYCLIC GUANOSINE ANALOGUES

In the drug group of acyclic guanosine analogues, there are six approved compounds: acyclovir, ganciclovir, valacyclovir (also known as valaciclovir), valganciclovir, penciclovir, and famciclovir (Fig. 11 and Table 2). Historically, acyclovir [9-((2-hydroxyethoxy)methyl)guanine] was first mentioned in a laboratory notebook of Nick Oliver in 1974 (245). Its antiviral properties were first uncovered by Peter Collins and John Bauer at the Wellcome Laboratories in Beckenham, United Kingdom. Acyclovir was originally designed as an inhibitor of adenosine deaminases to enhance the antiviral activity of vidarabine (246). Elion et al. (247) first pointed out that acyclovir owed its selectivity against HSV to specific phosphorylation by viral thymidine kinases. A few months later, acyclovir was reported to show potent activity against herpesviruses (HSV-1 and HSV-2) (248). This certainly was more of a surprise for a guanosine analogue (*viz.*, acyclovir) than for a 5-substituted 2′-deoxyuridine (*viz.*, BVDU). Acyclovir, targeting the viral DNA polymerase, was proven to be particularly active against HSV-1 and HSV-2 but much less so against VZV (249). Of the various acyclic guanosine analogues discovered subsequently, penciclovir was pursued for VZV infections, and ganciclovir became the drug of choice against HCMV infections (91). In clinical practice, ganciclovir is being gradually superseded by valganciclovir to treat HCMV infections, because valganciclovir seems to modestly improve hearing and developmental outcomes in the long term (250).

To increase oral bioavailability, the prodrug strategy was applied to all three acyclic nucleoside analogues, leading to the development of famciclovir, valacyclovir, and valganciclovir (245). For instance, famciclovir is the prodrug (diacetyl 6-deoxypenciclovir) of penciclovir. Acyclovir, ganciclovir, and penciclovir act in similar fashions and are all phosphorylated. Ganciclovir is specifically phosphorylated by host kinases (251), while acyclovir and

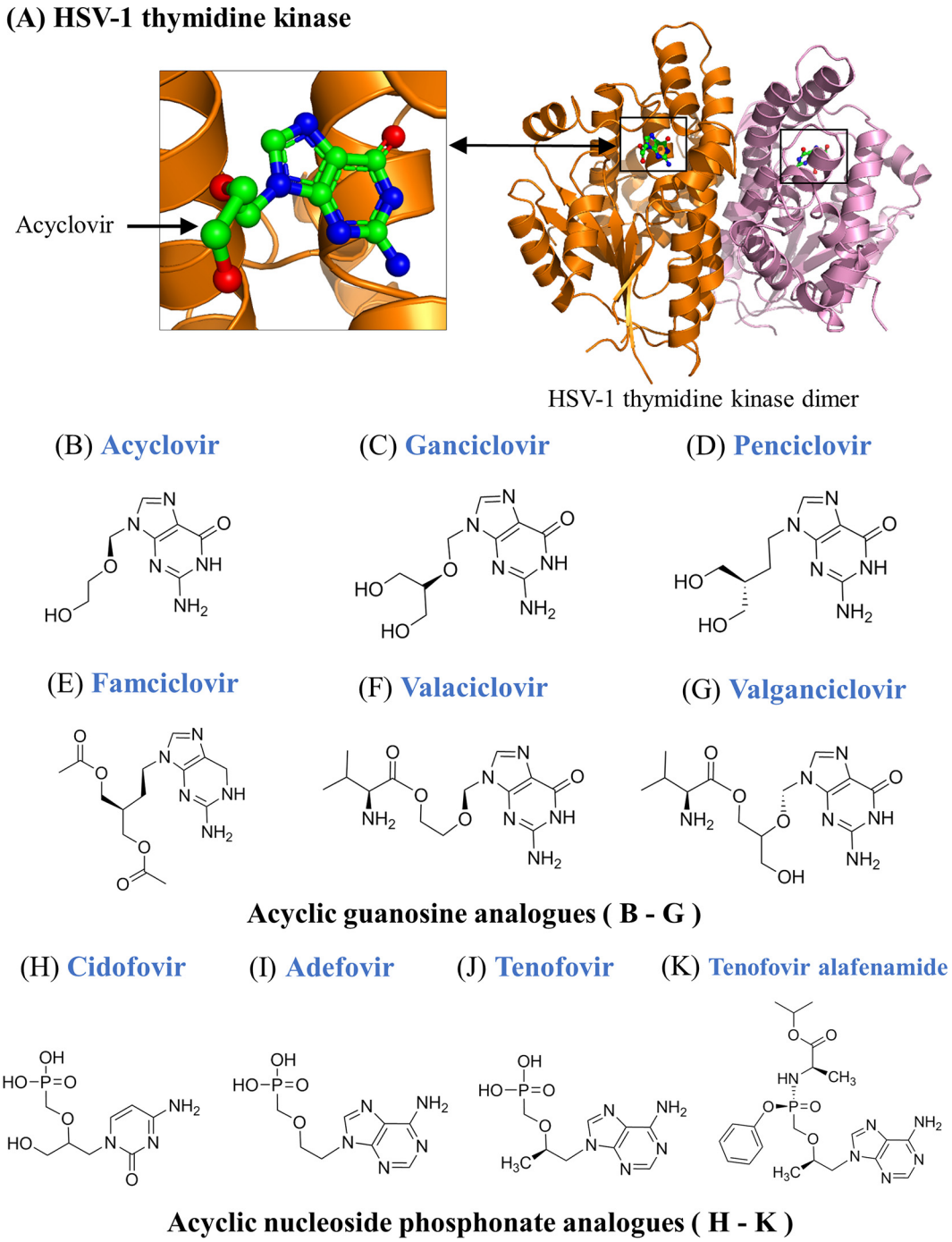

FIG 11 Tertiary structures of HSV-1 thymidine kinase and chemical formulas of acyclic guanosine analogues and acyclic nucleoside phosphonate analogues. (A) The HSV-1 thymidine kinase dimer in complex with acyclovir. Two units of thymidine kinase are shown in pink and orange, respectively. Acyclovir can be phosphorylated by HSV thymidine kinase and cellular enzymes (249). (B to G) Chemical formulas of acyclovir, famciclovir, valacyclovir, ganciclovir, penciclovir, and valganciclovir in the group of acyclic guanosine analogues. (H to K) Chemical formulas of cidofovir, adefovir, tenofovir, and tenofovir alafenamide in the group of acyclic nucleoside phosphonate analogues.

penciclovir are phosphorylated by viral thymidine kinases (247, 252) (Fig. 11). After their phosphorylation, acyclovir, ganciclovir, and penciclovir triphosphates individually compete with the natural substrate dGTP of viral DNA polymerases to inhibit viral DNA synthesis.

As of today, acyclovir continues to be the gold standard for the treatment of HSV infection. Despite the high efficacy of acyclovir, the mortality rate of patients with herpes simplex encephalitis who received acyclovir is ~14 to 19% (253). For patients treated with a standard course of intravenous acyclovir, a follow-up treatment with a 3-month course of valacyclovir is unlikely to provide added benefits compared to placebo (253). Nevertheless, owing to its

increased oral bioavailability, valacyclovir has superseded acyclovir for the treatment of HSV or VZV infections (254). In a recent study, an economic comparison between valacyclovir and valganciclovir was performed, suggesting that in the first year after renal transplantation, valganciclovir was more cost-effective than valacyclovir (255). On the other hand, famciclovir offers significant benefits, such as cost-effective therapy and accelerated rates of lesion resolution (256). For these reasons, famciclovir is now widely used to treat HSV or VZV infections.

ACYCLIC NUCLEOSIDE PHOSPHONATE ANALOGUES

In the drug group of acyclic nucleoside phosphonate (ANP) analogues, there are 10 FDA-approved (combination) drugs (Table 2). The ANP analogues that inhibit the activity of viral DNA polymerases come from the hybridization of (*S*)-DHPA [(*S*)-9-(2,3-dihydroxypropyl)adenine] with phosphonoacetic acid, thus generating (*S*)-HPMPA [(*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine]. Historically, the broad-spectrum antiviral activity of (*S*)-DHPA was first reported by De Clercq et al. (257), shortly after acyclovir had been described as a specific antiherpetic agent (248). In 1986, (*S*)-HPMPA was first reported as a new broad-spectrum anti-DNA virus agent by De Clercq et al. (258). Although (*S*)-HPMPA itself was not commercialized for clinical use, it could be considered the prototype ANP, from which emanated a series of ANP analogues, such as adefovir {PMEA [9-(2-phosphonomethoxyethyl)adenine]}, cidofovir {(*S*)-HPMPC [(*S*)-1-(3-hydroxy-2-phosphonomethoxypropyl)-cytosine]}, and tenofovir {(*R*)-PMPA [(*R*)-9-(2-phosphonomethoxypropyl)adenine]} (219, 259, 260) (Fig. 11). In June 1996, cidofovir was approved for the treatment of HCMV retinitis in AIDS patients (Table 2). Cidofovir has also been used as an off-label drug to treat many DNA virus infections such as HSV and adeno-, pox-, polyoma-, and papillomavirus infections (261). Later, adefovir was marketed in its oral prodrug form, adefovir dipivoxil (Hepsera), for the treatment of HBV infection, as was tenofovir, in its prodrug form, TDF (Viread), for the treatment of HIV and/or HBV infections.

In comparison to many TDF-based HIV therapies (Truvada, Atripla, Complera, and Stribild), recent clinical trials indicate that TDF monotherapy seems safe and effective against HBV infections (262–266). In comparisons of the effectiveness of TDF monotherapy versus dual therapies, it has been shown that TDF monotherapy is comparable to therapy with TDF plus (−)FTC (263, 267) or TDF plus ETV (268, 269), but it is less potent than TDF plus pegylated interferon alfa 2a (270). Because of its potency and high barrier to resistance, TDF monotherapy is currently recommended as the first-line treatment against chronic hepatitis B according to American Association for the Study of Liver Diseases (AASLD) guidelines (271), European Association for the Study of the Liver (EASL) guidelines (272), and WHO guidelines (114). As of April 2016, there has been no FDA-approved combination drug for HBV infections. Therefore, the optimal combination drug that achieves a sustained loss of serum hepatitis B virus surface antigen has yet to be discovered.

The concept for all ANPs is the same: it is based on the presence of a phosphonate (PCO) linkage (Fig. 11) instead of a normal phosphate (POC) linkage, which is a characteristic of nucleotide analogues against the activity of viral polymerases (273). The PCO linkage, in contrast with the POC linkage, cannot be cleaved by the hydrolase enzyme esterase. This fact explains the stability of the ANPs, as chain terminators, after their incorporation into the DNA chain (274). In the presence of the phosphonate group, ANPs can no longer be removed from the DNA chain, thereby leading to irreversible chain termination (259). Particularly, ANPs need to first be phosphorylated (by cellular enzymes) to become the diphosphate (not the triphosphate, as their phosphonate group mimics the 5′-monophosphate in the nucleotides). The following ANPs are, at present, on the market: (i) cidofovir (Vistide) (now generic), (ii) adefovir dipivoxil (Hepsera), (iii) TDF (Viread), (iv) TDF in combination with (−)FTC (Truvada), (v) TDF and (−)FTC in combination with efavirenz (Atripla), (vi) TDF and (−)FTC in combination with rilpivirine (Complera [United States] and Eviplera [European Union]), and (vii) TDF and (−)FTC in combination with elvitegravir and cobicistat (Stribild). It is worth mentioning that cidofovir may be replaced by its oral prodrug brincidofovir (originally referred to as hexadecyloxypropyl [HDP]-cidofovir) or CMX001 (193). Moreover, Viread has been approved for the treatment of HIV and/or HBV infections (Table 2). Truvada has been licensed for both therapy and prophylaxis of HIV infections. As for the combination drug Stribild, phase 3 clinical trials suggest that >90% of treatment-naive HIV-infected patients receiving Stribild may have virological success at 48 weeks (275). Moreover, Stribild is well tolerated in virologically suppressed adults infected with HIV-1 (276).

In November 2015, TAF (GS-7340) was approved in combination with cobicistat, emtricitabine, and elvitegravir (Genvoya) to treat HIV infections (Table 2). Genvoya is now on the market as a fixed-dose combination of TAF (10 mg), cobicistat (150 mg), emtricitabine (200 mg), and elvitegravir (150 mg). Three phase 3 clinical trials suggest that this combination drug could achieve virological success in 1,732 (94.9%) of 1,825 patients at 48 weeks of treatment (275, 277). Importantly, Genvoya provides a favorable safety profile because HIV-infected patients show fewer renal and bone effects after receiving Genvoya (275, 277).

Approved by the FDA in 2016, TAFs are now used in combination with (−)FTC (Descovy) or with (−)FTC plus rilpivirine (Odefsey) (Table 2). Forthcoming TAF-based drug combinations include (i) TAF in combination with (−)FTC plus efavirenz and (ii) TAF in combination with (−)FTC, elvitegravir, and cobicistat. These drugs combined with TAF have distinct advantages because they are specifically taken up by lymphocytes, and their dosages can be reduced by ~10-fold (278, 279). This benefit thus significantly reduces the risk of toxic effects such as kidney disturbances and bone demineralization (278, 279).

HCV NS5A/NS5B INHIBITORS

As of April 2016, there are 8 approved (combination) drugs in the group of HCV NS5A/NS5B inhibitors (Table 2). DAAs (direct-acting antivirals) for the treatment of HCV infections encompass, in principle, four classes: (i) NS3/4A protease inhibitors (Fig. 8), (ii) NS5A protein inhibitors (Fig. 12), (iii) NS5B polymerase inhibitors (Fig. 13) of the nucleoside/nucleotide type, and (iv) NS5B polymerase inhibitors of the nonnucleoside type (280). DAAs are now replacing the combination of pegylated interferons and ribavirin, the standard of care (SOC) for treating chronic HCV infections before 2013 (281).

HCV NS5A Inhibitors

As of April 2016, there are four approved NS5A inhibitors: daclatasvir, ledipasvir, ombitasvir, and elbasvir (Table 2). As illustrated in Fig. 12, daclatasvir can specifically bind to the HCV nonstruc-

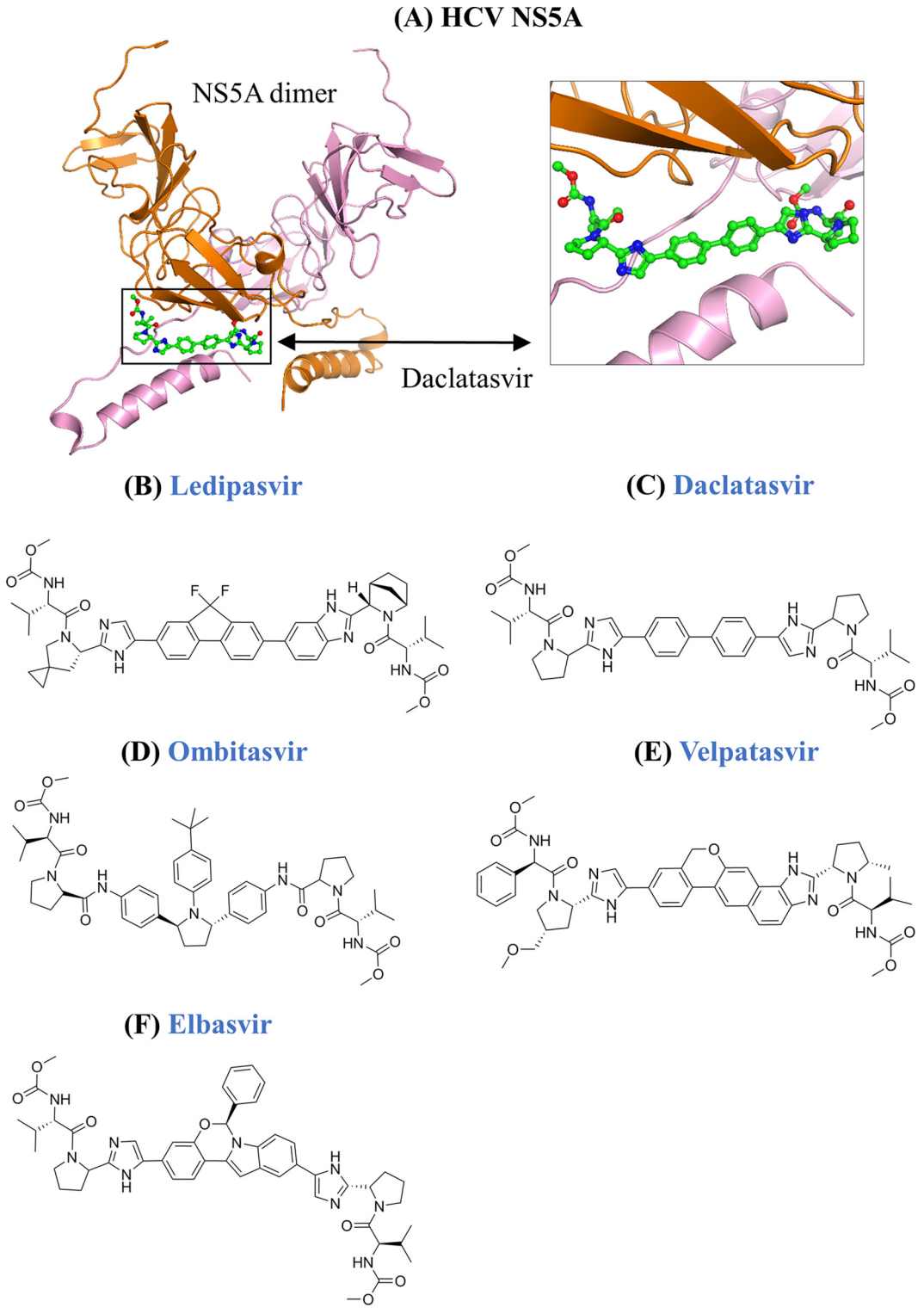

FIG 12 Tertiary structures of the HCV NS5A protein and chemical formulas of HCV NS5A inhibitors. (A) Tertiary structure of the HCV NS5A dimer in complex with daclatasvir. Two units of the HCV NS5A dimer are shown in pink and orange, respectively (PDB data were reported in reference 282). (B to F) Chemical formulas of ledipasvir, daclatasvir, ombitasvir, velpatasvir, and elbasvir in the group of HCV NS5A inhibitors. Note that velpatasvir is an experimental inhibitor currently in phase 3 clinical trials.

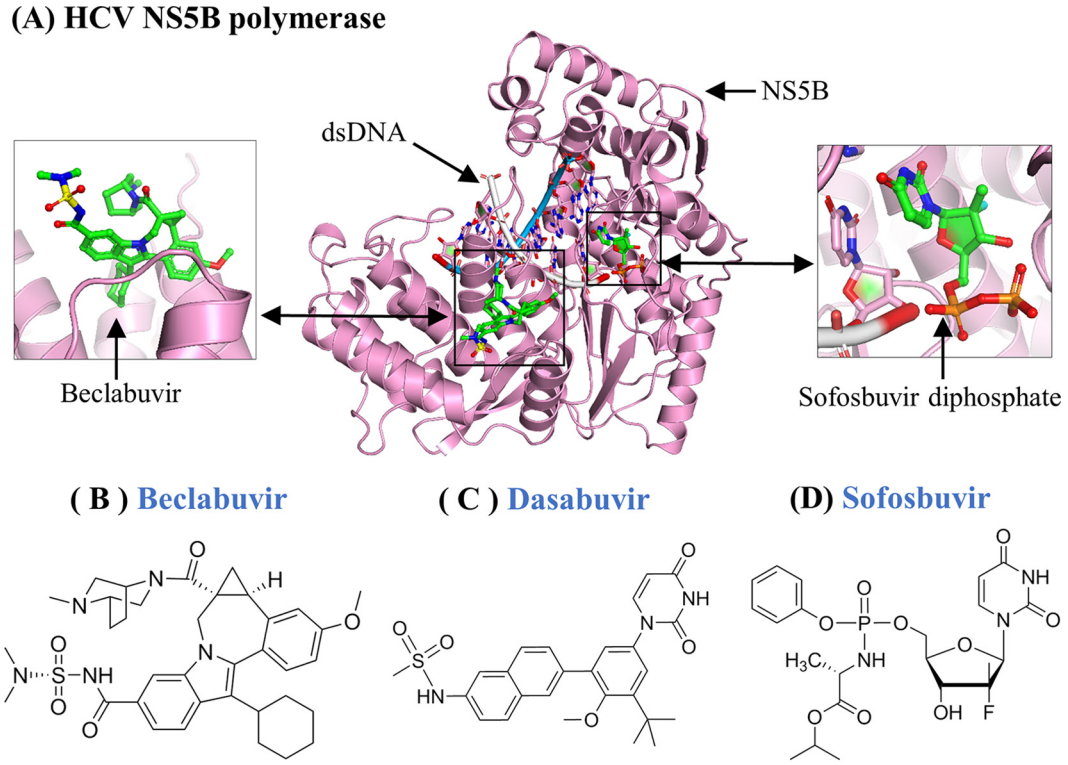

FIG 13 Tertiary structures of HCV NS5B polymerase and chemical formulas of HCV NS5B inhibitors. (A) Tertiary structure of HCV NS5B polymerase in complex with dsDNA, beclabuvir, and sofosbuvir diphosphate (PDB accession numbers 4NLD and 4WTG). Note that beclabuvir and sofosbuvir diphosphate bind to the allosteric site and the catalytic site of the HCV NS5B polymerase, respectively. (B to D) Chemical formulas of beclabuvir, dasabuvir, and sofosbuvir in the group of HCV NS5B inhibitors. Note that beclabuvir is a forthcoming inhibitor in the combination drug of daclatasvir plus asunaprevir plus beclabuvir in phase 4 clinical trials.

tural protein NS5A (282). The exact mechanisms of HCV NS5A drug action remain debated, especially regarding their potential inhibition of the structural stability, dimerization, or subcellular distribution of NS5A (283, 284). Nevertheless, NS5A inhibitors can block HCV RNA replication by interrupting the formation of the membranous web, a heterogeneous meshwork within cytoplasmic membranous factories where HCV replication takes place (284). Daclatasvir (Fig. 12) in combination with the protease inhibitor asunaprevir (Fig. 8) was approved in Japan, whereas the FDA has not yet granted its approval as of April 2016.

Recent clinical trials have demonstrated the effectiveness of daclatasvir plus asunaprevir. The phase 3 HALLMARK-DUAL trial enrolled patients with HCV genotype 1b infection, including 307 treatment-naive patients; 205 nonresponders; and 235 ineligible, intolerant, or ineligible and intolerant patients (285). The treatment outcome was measured by the rate of sustained virologic response at 12 weeks (SVR12). This study reported promising SVR12 rates (>80%) for daclatasvir (60 mg, once daily) plus asunaprevir (100 mg, twice daily) in the three patient groups mentioned above (285). A phase 3 clinical trial that enrolled 135 interferon-ineligible/intolerant patients and 87 nonresponder patients showed high SVR12 rates (>88%) for daclatasvir plus asunaprevir in the treatment of chronic HCV genotype 1b infection (286). Another clinical trial, which enrolled 230 patients with HCV genotype 1b infection, demonstrated that the efficacy-and-safety profile of daclatasvir plus asunaprevir was superior to that of telaprevir plus peginterferon plus ribavirin (287). Overall, given the 1,000 patients with HCV genotype 1b infection in the clinical trials mentioned above, treatment with daclatasvir (60 mg, once daily) plus asunaprevir (100 mg, twice daily) reached a high rate of SVR12 of up to 86.4% (n = 864). A phase 4 trial is currently ongoing to investigate the safety and efficacy of daclatasvir plus asunaprevir in patients with chronic hepatitis C infection and chronic renal failure (ClinicalTrials.gov registration number NCT02580474). Results of this clinical trial are to be released in 2017.

In January 2016, the once-daily fixed-dose combination of elbasvir plus grazoprevir (Zepatier) was approved by the FDA to treat HCV genotype 1 or 4 infection (Table 2). Elbasvir and grazoprevir inhibit HCV nonstructural protein NS5A (Fig. 12) and NS3/4A protease (Fig. 8), respectively. A number of clinical trials have been carried out to study the combination of grazoprevir plus elbasvir: (i) the phase 2 C-WORTHY trial, which enrolled 253 patients with HCV genotype 1 infection, showed high rates of sustained virologic response with treatment with grazoprevir plus elbasvir at 12 and 18 weeks in both treatment-naive patients with cirrhosis and patients with a previous null response to PegIFNα-2a plus ribavirin with or without cirrhosis (288); (ii) the phase 3 C-SURFER trial, which enrolled 224 patients with HCV genotype 1 infection and stage 4 to 5 chronic kidney diseases, suggested that treatment with grazoprevir plus elbasvir caused a low rate of adverse events and showed promising SVR12 rates (289); and (iii) the phase 3 C-EDGE trial demonstrated that grazoprevir plus elbasvir achieved high rates of SVR12 in 421 treat-

ment-naive and noncirrhotic patients infected with HCV genotype 1, 4, or 6 (290). In these clinical trials, common side effects such as headache, nausea, and fatigue were recorded (289, 290). Given the 484 patients infected with HCV genotype 1 or 4 in three clinical trials (C-WORTHY, C-SURFER, and C-EDGE), the combination of grazoprevir (100 mg) plus elbasvir (50 mg) showed a success rate of SVR12 of up to 95.8% ($n = 464$). However, the efficacy of grazoprevir plus elbasvir in HCV genotype 6 infection has yet to be clarified, because the C-EDGE study showed SVR12 for only 8 out of 10 patients (290). Overall, the combination of grazoprevir (100 mg) plus elbasvir (50 mg) has been shown to be an effective pangenotypic drug (Zepatier) against HCV genotype 1 or 4 infection.

HCV NS5B Inhibitors

For the "nonnucleoside" NS5B polymerase inhibitors (Fig. 13), sofosbuvir and dasabuvir have been approved by the FDA (Table 2), while a number of experimental inhibitors (i.e., deleobuvir, setrobuvir, beclabuvir, and tegobuvir) have been identified to target allosteric sites of the HCV NS5B polymerase (178, 179). The list of "nucleoside" NS5B polymerase inhibitors is so short because several compounds were discontinued prematurely due to undesirable side effects. Sofosbuvir is, however, an exception in this group, which did not reveal toxicity or drug resistance, and it could be administered with other HCV drugs in combination as a single oral pill for a total duration of 12 weeks, guaranteeing a high level of sustained virologic response (291). To pursue interferon-free treatment, sofosbuvir could be combined with an NS5A inhibitor, such as ledipasvir (292). This combination has been dubbed Harvoni, which is administered as a once-daily oral pill containing sofosbuvir (400 mg) and ledipasvir (90 mg). With this combination, the treatment duration could eventually be shortened to <12 weeks (293), providing high rates of sustained virologic response in patients coinfected with HIV-1 and HCV genotype 1 or 4 (294).

To obtain clearance, a real "cure" of a chronic virus infection, as noted for HCV, is unheard of in the medical history of infectious diseases and sharply contrasts with the situation for HIV and HBV infections. In principle, current development of anti-HIV drugs requires lifelong treatments, while anti-HBV therapies may lead to a real cure only in a small percentage of HBV-infected patients (295, 296).

INFLUENZA VIRUS INHIBITORS

As of April 2016, 8 drugs have been approved to treat influenza infections (Table 2). As illustrated in Fig. 14, these drugs could be recognized as matrix 2 inhibitors (amantadine and rimantadine), neuraminidase inhibitors (zanamivir, oseltamivir, peramivir, and laninamivir octanoate), and polymerase inhibitors (ribavirin and favipiravir). We describe the details of these drugs below.

Amantadine and Rimantadine

Amantadine (1-adamantanamine) was the first antiviral compound approved in 1966 to treat influenza A virus infections (297). This compound blocks the transport of H^+ ions through the M2 (matrix 2) protein channels (Fig. 14) into the interior of viral particles, thus preventing the uncoating of influenza virus particles within the endosomes (298, 299) (Fig. 4). After the discovery of amantadine, rimantadine and a number of amantadine derivatives were later synthesized (300, 301), but they did not reach the market, except for amantadine and rimantadine. Despite their approval for adult patients, amantadine and rimantadine do not contribute to the prevention, treatment, or reduced duration of influenza A virus infection in children and the elderly (302). Because of widespread resistance, amantadine has virtually been abandoned in the treatment of influenza infections (303). However, there is growing interest for the use of amantadine in the early symptomatic treatment of Parkinson disease and levodopa-induced dyskinesia (304, 305). More clinical evidence is required to prove this new application of amantadine.

Zanamivir, Oseltamivir, Peramivir, and Laninamivir Octanoate

The rational computer-aided design of zanamivir (306) marked a new era in antiviral drug development (300). As a highly selective inhibitor of influenza A and B virus neuraminidases (Fig. 14), zanamivir prevents influenza infections by impeding virus release rather than virus entry or other viral stages during the viral life cycle (307) (Fig. 4). Zanamivir administered by inhalation was soon joined by oseltamivir, which could be administered by the oral route (308). Oral oseltamivir and inhaled zanamivir can offer net benefits by reducing mortality and the duration of influenza symptoms and complications, according to a systematic review and meta-analysis of 74 observational studies (309). Soon after the success of zanamivir and oseltamivir, two neuraminidase inhibitors were later launched for the treatment of influenza infections (310): peramivir, which could be given as a single intravenous injection (311), and laninamivir octanoate, which would be effective if given as a single inhalation (312). Notably, peramivir has clinical efficacy similar to that of oseltamivir in the treatment of severe seasonal influenza (313), while the potency of laninamivir octanoate has been shown for the treatment of seasonal influenza, including oseltamivir-resistant virus, in adults (312). Intravenous peramivir and inhalational laninamivir are used as a single-dose treatments for influenza A and B viruses, but this application is limited in a few countries (laninamivir in Japan and peramivir in the United States, Japan, South Korea, and China) (314).

Ribavirin

Ribavirin (Virazole), 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, is the first synthetic nucleoside analogue that has ever been reported to be active against a broad spectrum of RNA viruses (HCV, RSV, and influenza virus): "its antiviral spectrum was the broadest ever reported for a synthetic material that did not induce interferon" (315). Its principal mechanism of drug action, established shortly after the discovery of ribavirin (316), is the inhibition of inosine-5′-monophosphate (IMP) dehydrogenase, which converts IMP to xanthosine monophosphate (XMP) and thus accounts for the *de novo* biosynthesis of GTP (317). The inhibitory activity of ribavirin on the IMP dehydrogenase may contribute to the immunosuppressive effects of ribavirin (318). This in turn contributes to the significant success obtained by ribavirin, in combination with peginterferon alfa 2a, for the treatment of HCV infection (319, 320). HCV-infected patients who received treatments of telaprevir, peginterferon alfa 2a, and ribavirin had a significant level of sustained virologic response (321). Approved for influenza treatment, ribavirin in the triphosphate form efficiently inhibits the RNA polymerase of influenza virus (322). Besides, ribavirin is used in the therapy of some hemorrhagic fever virus infections (e.g., Lassa fever [323]), but ribavirin

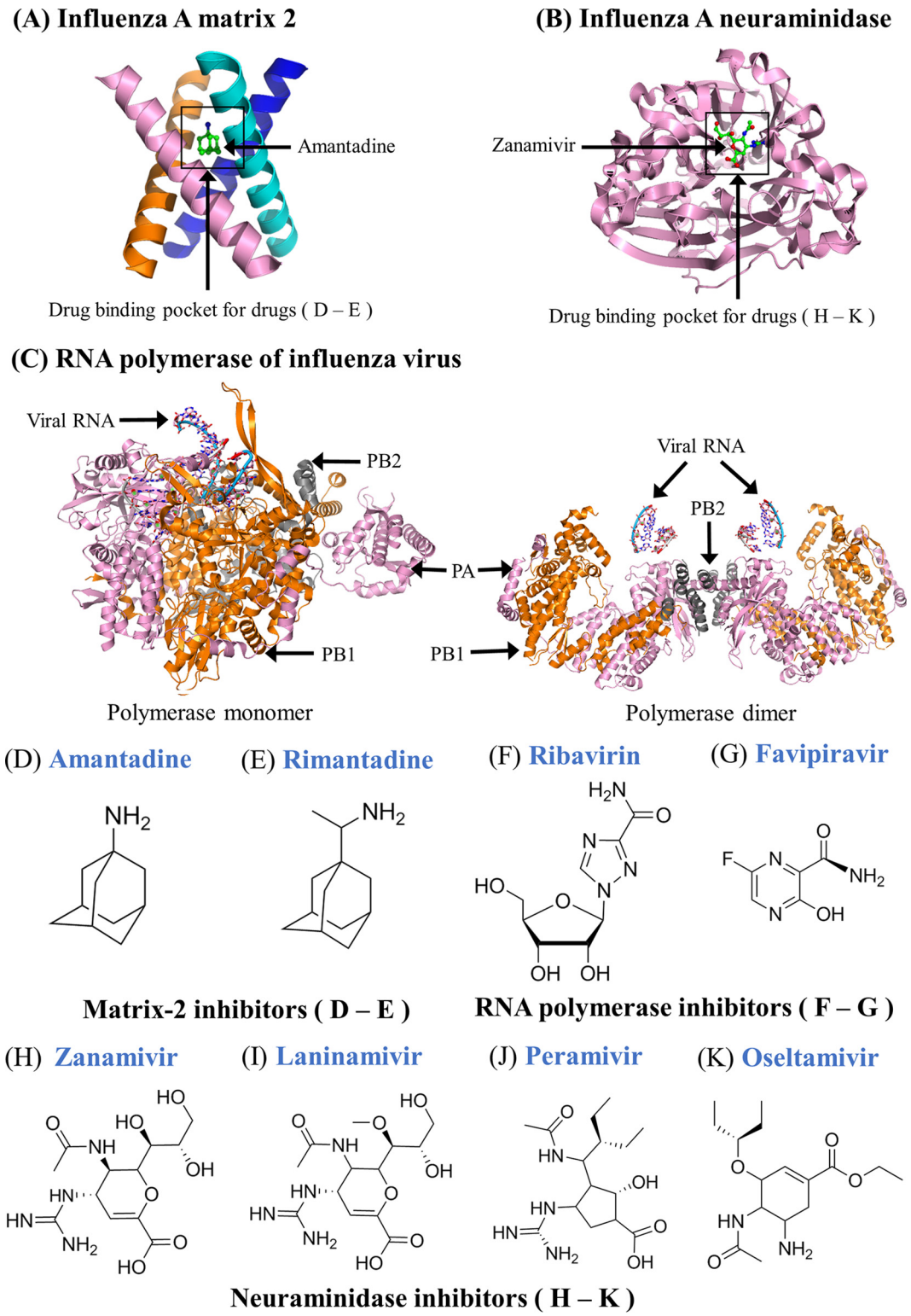

FIG 14 Tertiary structures of influenza virus proteins (matrix 2, neuraminidase, and RNA polymerase) and chemical formulas of influenza virus inhibitors. (A) Tertiary structure of the influenza A virus matrix 2 protein in complex with amantadine (PDB accession number 2KAD). Movies that simulate the binding of approved antiviral drugs to viral or host proteins are available online (see http://www.virusface.com/). (B) Structure of influenza A virus neuraminidase in complex with zanamivir (PDB accession number 2HTQ). (C) Tertiary structure of influenza virus RNA polymerase in complex with RNA. The RNA polymerases of influenza A virus (left) (PDB accession number 3J9B) and influenza B virus (right) (PDB accession number 4WRT) are illustrated. The PA, PB1, and PB2 subunits of RNA polymerase (see structural details in reference 480) are shown in pink, orange, and gray, respectively. Ribavirin triphosphate targets the catalytic site of the RNA polymerase to inhibit viral replication. Note that the RNA polymerase of influenza A virus is a tetramer (480), but the complete tetramer structure of influenza virus RNA polymerase in complex with its inhibitors is still lacking. (D and E) Chemical formulas of amantadine and rimantadine, which target the matrix 2 protein of influenza virus. (F and G) Chemical formulas of ribavirin and favipiravir, which target the viral RNA polymerase of influenza virus. (H to K) Chemical formulas of zanamivir, laninamivir, peramivir, and oseltamivir, which target the viral neuraminidase of influenza virus.

has never been formally licensed for this medication. The potential activity of ribavirin against RNA viruses has also been shown in the search for antiviral candidates against many emerging infectious diseases such as dengue virus (324), norovirus (325, 326), Marburg virus (MARV) (327), and Hendra and Nipah viruses (328). Nevertheless, more clinical evidence is still required to prove these new applications.

Favipiravir

Favipiravir (also known as T-705), 6-fluoro-3-hydroxy-2-pyrazine carboxamide (Fig. 14), has been primarily pursued for the treatment of influenza infections (329–331). Approved in Japan, favipiravir can be used in the treatment of influenza A, B, and C virus infections (Table 2). According to the mechanism of drug action postulated by Furuta et al. (332), favipiravir is converted intracellularly to its ribofuranosyl monophosphate form by the phosphoribosyl transferase; two phosphorylations subsequently convert the ribofuranosyl monophosphate form to the triphosphate form, the active metabolite of favipiravir. Importantly, favipiravir triphosphate shows broad-spectrum inhibitory activities against the RNA polymerases of influenza A viruses (including the highly pathogenic H5N1 viruses) (330, 333) and many other positive-sense RNA and negative-sense RNA viruses (331). Recently, favipiravir has been proposed to treat patients infected with Ebola virus (EBOV) (334). Preliminary results suggest that favipiravir efficiently inhibits Ebola virus infections in mouse models (335, 336), but further investigations are still needed (337). In addition, favipiravir can inhibit the replication of human norovirus (325, 326) and human arenaviruses (Junin, Machupo, and Pichinde viruses) (338, 339), but these new applications require further evidence from clinical trials.

INTERFERONS, IMMUNOSTIMULATORS, OLIGONUCLEOTIDES, AND ANTIMITOTIC INHIBITORS

In the drug group of interferons, immunostimulators, oligonucleotides, and antimitotic inhibitors, there are 8 FDA-approved drugs: (i) interferons for HBV and/or HCV infections; (ii) fomivirsen (an antisense oligonucleotide) for HCMV infections; and (iii) podofilox (an antimitotic inhibitor), imiquimod (an immunostimulator), and sinecatechins (a botanical drug) for the treatment of external genital warts caused by HPV infections (Table 2). These approved drugs share one thing in common: they exert specific inhibitory effects without targeting viral proteins directly. Below, we describe the details of these drugs.

Interferons

To treat HBV or HCV infections, three interferons have been licensed: interferon alfacon 1, pegylated interferon alfa 2a (PegIFNα-2a), and PegIFNα-2b (Table 2). Due to its severe adverse events, interferon alfacon 1 has been discontinued since September 2013. Currently, PegIFNα-based regimens are preferably used for HBV but not for HCV infections, because interferon-free drugs are now effective against HCV infections (340). Interferon alpha (IFNα), predominantly secreted by hematopoietic cells (e.g., plasmacytoid dendritic cells), is a well-defined type I interferon that stimulates the immune system for antiviral defense (341–343). To increase the half-life of interferon inhibitors in serum, polyethylene glycol polymers are covalently attached to IFN-α for the production of PegIFNα. Interestingly, there is only one amino acid at position 23 that distinguishes human IFNα-2a (hIFNα-2a) from hIFNα-2b (K23 in hIFNα-2a and R23 in hIFNα-2b) (Fig. 15). Regarding the mechanism of drug action, PegIFNα-2a and PegIFNα-2b mainly interfere with viral replication in two aspects. First, they stimulate immunity cells ($CD8^+$ cells and natural killer T cells) to enhance the noncytolytic clearance of viruses by cytokines or cytolysis of infected cells (344). Second, they stimulate the expression of innate antiviral genes and proteins (e.g., APOBEC3A/B and MxA) to block viral replication (344).

In clinical practice, interferon-based treatments are infrequently used due to their multiple side effects, high costs, and inconvenience of administration (345). Importantly, a wide range of side effects with PegIFNα have been reported: fever, fatigue, bone marrow suppression, influenza-like symptoms, depression, and exacerbation or development of autoimmune illnesses (346). For this reason, PegIFNα-2a has been approved only for HBV-infected adults (180 μg/week for 48 weeks) but not for children (114, 271). Moreover, it remains debatable whether interferons should or should not be combined with other antiviral compounds (e.g., lamivudine, adefovir dipivoxil, TDF, or entecavir) (347–349). For instance, PegIFNα-2a plus adefovir dipivoxil may increase HBV-specific T cell restoration (349), whereas PegIFNα-2a with TDF-based therapies at 48 weeks does not increase the seroconversion rate of HBeAg-positive patients coinfected with HBV and HIV (350). Furthermore, PegIFNα-2a should not be used with telbivudine due to an increased risk of peripheral neuropathy (351). The added value of interferons in combination with nucleos(t)ide analogues warrants further investigation.

Immunostimulatory and Antimitotic Inhibitors

Approved by the FDA in February 1997, 5% imiquimod cream (Aldara) is a patient-applied immune response modifier for the treatment of external genital warts caused by HPV infections (352, 353). Imiquimod, 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine (also known as R-837 and S-26308), is a nonnucleoside heterocyclic amine (Fig. 15). Although its antiviral activity could not be shown by *in vitro* experiments, imiquimod stimulates macrophages to secrete cytokines (e.g., interferon alpha, tumor necrosis factor alpha [TNF-α], interleukin-1 [IL-1], IL-6, and IL-8) for wart regression and local inflammatory reactions (352, 354). Clinical trials suggested that 5% imiquimod cream was safe and well tolerated in the treatment of external genital warts (352, 353, 355). Moreover, it is applied 3 times per week until complete clearance is achieved or for a maximum of 16 weeks, and the most common side effects are skin reactions (e.g., itching, burning, and erythema). Clearance rates with 5% imiquimod cream vary from 37% to 50%, and the recurrence rate is ~13% (356).

A 15% sinecatechin ointment (Veregen) is the first FDA-approved botanical drug for the topical treatment of external genital warts (357). The name sinecatechins originates from the Latin name for Chinese green tea (*Camellia sinensis*) and its major chemical components (catechins) (357). Veregen is a purified product of catechins from leaves of Chinese green tea containing >80% catechins and polyphenols. Importantly, catechins (Fig. 15) are known for their antiangiogenic activity, anti-inflammatory and immunostimulatory activities, and antimicrobial potential (358). Two phase 3 clinical studies suggest that 15% sinecat-

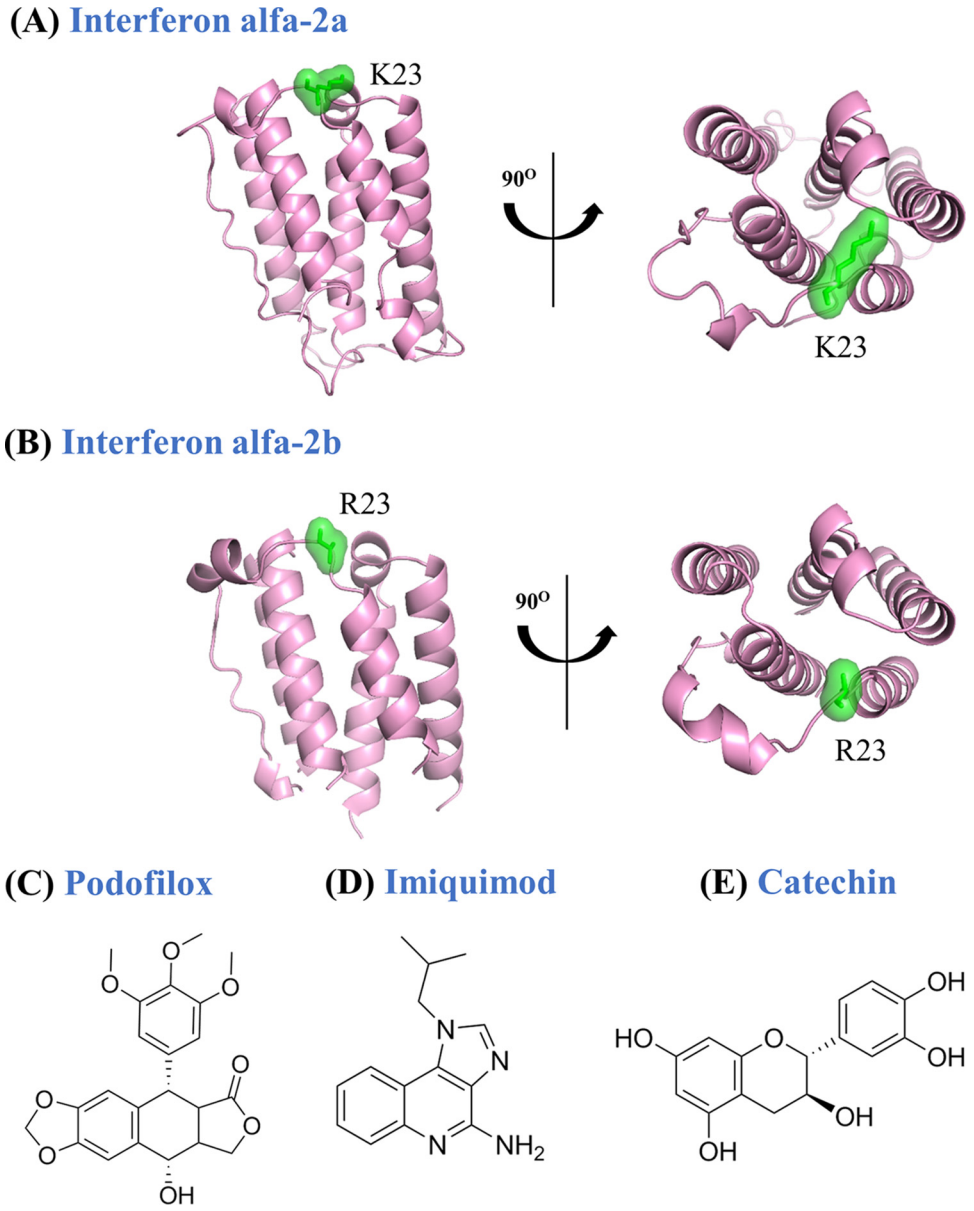

FIG 15 Tertiary structures of interferons and chemical formulas of podofilox, imiquimod, and catechin. (A and B) Cartoon representations of interferon alfa 2a (PDB accession number 4YPG) and interferon alfa 2b (PDB accession number 1RH2). Sequence comparison suggests that amino acid K23 in interferon alfa 2a and amino acid R23 in interferon alfa 2b mark the only sequence difference between interferon alfa 2a and interferon alfa 2b. Structural movies are available online (http://www.virusface.com/). (C to E) Chemical formulas of podofilox, imiquimod, and catechin. Note that catechin is the major ingredient of the botanical drug sinecatechin.

echin ointment is a well-tolerated, self-applicable, and effective topical treatment to clear external genital warts (359, 360). The most common side effects with sinecatechins are local skin and application site reactions (e.g., erythema, pruritus, burning, pain, and erosion). The clearance rate with 15% sinecatechin ointment reaches ~54%, and the recurrence rate is ~7% at 12 weeks (356).

Podofilox (Condylox) is an antimitotic compound purified from crude podophyllum resin within the roots and rhizomes of May apple or podophyllum plant (either North American *Podophyllum peltatum* or Indian *Podophyllum emodi*) (361). Podofilox is safe and effective in the treatment of external genital warts but not mucous membrane warts (361, 362). Instead of targeting HPV proteins directly, podofilox is a cytotoxic drug with specific pharmacological actions against the formation of the mitotic spindle at metaphase, leading to the interruption of cell division (362, 363). Two topical treatments are currently approved for self-applicable administration: a 0.5% podofilox solution and a 0.5% podofilox gel. In particular, podofilox is applied when the areas of external warts are <10 cm^2. The internal use of podofilox in either the vagina or the anus is not recommended. The most common side effects with podofilox are inflammation, burning, erosion, pain, or itching (364). Clearance rates with the 0.5% podofilox solution vary from 45% to 77%, and the recurrence rates are between 4% and 33% (356).

Antisense Oligonucleotides

Fomivirsen (Vitravene) is the first FDA-approved antisense oligonucleotide harboring a 21-nucleotide phosphorothioate oligonucleotide (5′-GCG TTT GCT CTT CTT CTT GCG-3′) (365). Based on its antisense mechanism, fomivirsen is complementary to a sequence in mRNA encoding major immediate early region 2 of HCMV; thus, the binding of fomivirsen to this region inhibits the gene expression of essential HCMV proteins (366). Fomivirsen sodium, administered as an intravitreal injection into human eyes, has been approved for treating HCMV retinitis in patients infected with AIDS (367). Despite the fact that it is well tolerated and has a favorable safety profile (368), intravitreous fomivirsen has been discontinued for commercial reasons.

FORTHCOMING ANTIVIRAL INHIBITORS

In addition to the 90 approved antiviral drugs, many experimental inhibitors have been under investigation in phase 3 clinical trials (http://www.clinicaltrials.gov/). For instance, besifovir is an HBV inhibitor showing an efficacy similar to that of the approved inhibitor entecavir (369), but its safety is worrying (370). As the first thiazolide in clinical trials, nitazoxanide may inhibit chronic HCV (371), whereas more randomized clinical trials with a low risk of bias are still needed (372). Development of many antiviral inhibitors still depends on the results of phase 3 trials, such as human monoclonal antibody REGN2222 against RSV (373) (ClinicalTrials.gov registration number NCT02325791), the HIV NNRTI doravirine (374) (registration number NCT02397096), and the HIV integrase inhibitor GS-9883 (registration numbers NCT02607930, NCT02607956, NCT02603120, and NCT02603107). Here, we provide an overview of four forthcoming antiviral drugs: (i) sofosbuvir plus velpatasvir for treatment of infections by HCV genotypes 1 to 6, (ii) daclatasvir plus asunaprevir with or without beclabuvir for treatment of HCV genotype 1 infections, (iii) FV100 for treatment of VZV infections, and (iv) letermovir for treatment of HCMV infections (Table 3).

Sofosbuvir plus Velpatasvir

The combination of sofosbuvir (400 mg) plus velpatasvir (100 mg) has been recognized as an effective pangenotypic therapy against infections by HCV genotypes 1 to 6 (375, 376). Sofosbuvir is an approved nucleoside compound that inhibits HCV NS5B polymerase activities (Fig. 13), while velpatasvir is an experimental inhibitor targeting HCV nonstructural protein NS5A (Fig. 12). HCV pangenotypic drugs may require no genotyping tests and potentially offer the simplest "test-and-cure" strategy to eliminate HCV infections (375). Supported by successful clinical trials, the once-daily fixed-dose combination of sofosbuvir plus velpatasvir was submitted to the FDA as a new drug application on 28 October 2015.

A number of clinical trials have been carried out to study the combination drug of sofosbuvir plus velpatasvir: (i) the ASTRAL-1 trial, which enrolled 740 HCV-infected patients with noncirrhotic or compensated cirrhosis, demonstrated the effectiveness of the combination of sofosbuvir plus velpatasvir against HCV genotype 1, 2, 4, 5, or 6 (377); (ii) the ASTRAL-2 and ASTRAL-3 trials, which enrolled 266 and 552 patients, respectively, suggested that therapy with sofosbuvir plus velpatasvir was superior to therapy with sofosbuvir plus ribavirin for treatment of infection by HCV genotype 2 or 3 (376); (iii) the ASTRAL-4 trial further revealed that sofosbuvir plus velpatasvir achieved high rates of SVR12 in 267 patients with HCV infection (genotypes 1 to 6) and decompensated cirrhosis (378); and (iv) two randomized clinical trials, which enrolled 321 and 377 patients, respectively, suggested that treatment with sofosbuvir (400 mg) plus velpatasvir (100 mg) provided remarkable rates of SVR12 in treatment-naive or treatment-experienced patients infected with HCV genotypes 1 to 6 (379, 380). The combination treatment in these clinical trials gave rise to common side effects such as fatigue, headache, insomnia, or nausea (376, 378–380). Nevertheless, given the 1,254 patients infected with HCV genotypes 1 to 6 in the six clinical trials described above, treatment with sofosbuvir (400 mg, once daily) plus velpatasvir (100 mg, once daily) showed a success rate of SVR12 of up to 97.4% ($n = 1,221$).

Daclatasvir plus Asunaprevir with or without Beclabuvir

To treat HCV genotype 1 or 4 infection, phase 3 clinical trials were established to study (i) a fixed-dose combination of daclatasvir (60 mg, once daily) plus asunaprevir (100 mg, twice daily) (285) and (ii) a twice-daily fixed-dose combination of daclatasvir (30 mg) plus asunaprevir (200 mg) plus beclabuvir (75 mg) (381, 382). Daclatasvir is an FDA-approved inhibitor targeting HCV NS5A (Fig. 12), and beclabuvir is an experimental inhibitor targeting HCV NS5B (Fig. 13). The combination of the HCV protease inhibitor asunaprevir with daclatasvir was approved in Japan, but the FDA has not approved this combination as of April 2016.

The effectiveness of daclatasvir plus asunaprevir plus beclabuvir has been demonstrated in recent clinical trials: (i) the phase 2 AI443014 trial, which enrolled 187 patients with HCV genotype 1 infection, revealed that the virologic response with daclatasvir plus asunaprevir plus beclabuvir (75 mg) was higher than that with daclatasvir plus asunaprevir plus beclabuvir (150 mg) (381); (ii) the phase 3 UNITY-1 trial, which enrolled 312 treatment-naive and 103 treatment-experienced noncirrhotic patients infected with chronic HCV genotype 1, suggested that daclatasvir plus asunaprevir plus beclabuvir achieved high rates (>89%) of SVR12 (382); and (iii) the phase 3 UNITY-2 trial, which enrolled 112 treatment-naive and 90 treatment-experienced patients infected with chronic HCV genotype 1 and with compensated cirrhosis, suggested that daclatasvir plus asunaprevir plus beclabuvir achieved promising rates (>85%) of SVR12 (383). The most common side effects with this combination drug were headache, diarrhea, fatigue, and nausea (381, 382). Given the 597 patients with HCV genotype 1 infection in the clinical trials described above, treatment with daclatasvir (30 mg) plus asunaprevir (200 mg) plus beclabuvir (75 mg) showed a success rate of SVR12 of up to 91.5% ($n = 546$).

FV100

FV100 (FV for FermaVir) has been developed as an effective, well-tolerated, once-daily treatment for herpes zoster or shingles, a painful rash caused by VZV infections (384). FV100 is a lipophilic bicyclic nucleoside analogue (Fig. 5) that inhibits the activity of the VZV DNA polymerase (385). *In vitro* experiments on VZV-infected cells at day 3 postinfection demonstrated that FV100 efficiently inhibited VZV replication at a 50% effective concentration (EC_{50}) of 0.09 μM, which was more potent than BVDU (EC_{50} of 0.9μM) and acyclovir (EC_{50} of 9μM) (386).

A phase 1 study, which enrolled 107 VZV-infected patients (384), concluded that once-daily oral dosing of FV100 could be sufficient to maintain the drug concentration above the EC_{50} *in*

vivo, and FV100 was well tolerated in elderly and young patients (385, 387). A phase 2 clinical trial, which enrolled 329 patients aged 50 years and older, evaluated the incidence of postherpetic neuralgia (PHN) for treatment with FV100 versus valacyclovir at 90 days. The PHN incidence rates with 200 mg FV100 (17.8%; 19/107) and 400 mg FV100 (12.4%; 14/113) were lower than that with 1,000 mg valacyclovir (20.2%; 22/109) (Contravir). To compare 400 mg FV100 with 1,000 mg valacyclovir, results of a phase 3 trial recruiting 985 patients will be released by the end of 2016 (ClinicalTrials.gov registration number NCT02412917).

Letermovir

Letermovir (MK-8228 or AIC246) is a 3,4-dihydro-quinazoline-4-yl-acetic acid derivative that targets the pUL56 subunit of the HCMV terminase complex to block viral DNA processing and/or packaging (388–390). Based on *in vitro* experiments, letermovir showed promising antiviral activity in different cell lines in comparisons of letermovir (EC_{50} of 0.0035 to 0.0056 μM) versus ganciclovir (EC_{50} of 0.32 to 2.39 μM) (391). The first proof-of-concept trial, which enrolled 27 transplant recipients with active HCMV infections, identified virus clearance in 6 of 12 patients (50%) who received 14 days of letermovir, in comparison to 2 of 7 patients (28.6%) who received the local standard of care (67). A phase 2 clinical trial, which enrolled 131 HCMV-seropositive allogeneic hematopoietic stem cell transplant recipients, demonstrated that the incidence of HCMV infection in patients who received once-daily doses of 240 mg letermovir (29%; 10/34) at 12 weeks was significantly lower than that in patients who received placebo (64%; 21/33) (392). In this phase 2 clinical trial, the letermovir resistance mutation V236M was identified in patients who failed treatment with a suboptimal letermovir concentration of 60 mg, but treatment with 240 mg letermovir at 12 weeks achieved complete suppression of viremia (393).

Letermovir at 240 mg had significant anti-HCMV activity, with an acceptable safety profile (392). Gastrointestinal disorders, including diarrhea, nausea, and vomiting, were common side effects in the phase 2 clinical trial (392). An ongoing phase 3 clinical trial, enrolling about 540 HCMV-seropositive allogeneic hematopoietic stem cell transplant recipients, will show the efficacy and safety of 240 mg letermovir in preventing HCMV infections 24 weeks after transplant actions (ClinicalTrials.gov registration number NCT02137772). Results of this clinical trial will be released in 2017.

ANTIVIRAL STRATEGIES AGAINST CURRENT AND EMERGING INFECTIOUS DISEASES

Emerging viral infections (e.g., Zika virus, dengue virus, and Ebola virus [EBOV]) are afflicting millions of humans worldwide. For this reason, there is growing interest in developing new treatments against emerging infectious diseases (394). Here, we highlight antiviral strategies against 41 infectious diseases. For convenience, we categorize these viruses into four groups: (i) viruses ($n = 4$) targeted by both approved vaccines and antiviral drugs, (ii) viruses ($n = 5$) targeted by approved antiviral drugs but not by vaccines, (iii) viruses ($n = 13$) targeted by approved vaccines but not by antiviral drugs, and (iv) viruses ($n = 19$) targeted by neither approved vaccines nor antiviral drugs.

Viruses Targeted by both Antiviral Drugs and Vaccines

As of April 2016, the FDA has approved vaccines and antiviral drugs to treat HBV, HPV, VZV, and influenza viruses. In addition to the antiviral drugs summarized above, here, we briefly describe FDA-approved vaccines.

HBV vaccines. Three HBV vaccines (Pediarix, Engerix-B, and Recombivax HB) have been approved for all HBV genotypes. The effectiveness of universal HBV immunization in preventing chronic hepatitis B infections is ~90 to 95% (395). Due to the success of HBV vaccines, the rate of global HBV vaccine coverage is ~75%, and this rate is much higher in developed countries (89% in the United States and 91% in the Western Pacific) (395).

VZV vaccines. As two live-attenuated VZV vaccines, Zostavax and Varivax were licensed against varicella in 1995 and against herpes zoster in 2006, respectively (80). Herpes zoster vaccines can efficiently protect older adults from herpes zoster diseases (396). The mean effectiveness of a single dose of the varicella vaccine is ~80 to 85% against all levels of disease severity (397).

HPV vaccines. Three vaccines have been approved for different HPV types: Cervarix for HPV-16 and HPV-18, Gardasil 9 for HPV-9, and Gardasil for HPV-6, HPV-11, HPV-16, and HPV-18. Routine vaccination using either Gardasil or Cervarix is currently recommended (398).

Influenza virus vaccines. The FDA has approved (i) monovalent vaccines for influenza A (influenza A [H5N1] virus monovalent vaccine and influenza A [H1N1] 2009 virus monovalent vaccines), (ii) trivalent vaccines for influenza A and B viruses (Afluria, Agriflu, Fluad, Fluarix, Flublok, Flucelvax, FluLaval, Fluvirin, and Fluzone), and (iii) quadrivalent vaccines for influenza A and B viruses (FluMist, Fluarix, Fluzone, and FluLaval). Apart from their important roles against viral infections, influenza vaccines have their limitations (399, 400). First, after influenza vaccination, it takes up to 2 weeks in adults and 6 weeks in children to develop immunity. Patients might be vulnerable within this period. Second, the effectiveness of influenza vaccination is impaired by many factors (e.g., vaccine mismatch, immunosuppression, or lack of compliance). Third, due to emerging influenza virus strains, a new vaccine may not be available for periods of up to several months, and not all patients could be vaccinated in a time of need. Therefore, additional coverage by antiviral drugs (i.e., neuraminidase inhibitors) is still required. The significant variation of influenza virus strains may cause resistance to antiviral agents; thereby, optimal antiviral treatments are yet to be discovered (399, 401).

Viruses Targeted by Antiviral Drugs but Not by Vaccines

As of April 2016, the FDA has approved antiviral drugs for the treatment of HIV, HCV, HSV, RSV, and HCMV, but their vaccines are still lacking: (i) HIV and HCV vaccines are not available and will be unlikely to be available in the foreseeable future, so treatments of these infections depend solely on effective antiviral drugs that are currently available; (ii) although an effective HSV vaccine is still lacking, many HSV vaccine candidates (e.g., HSV529) are currently being tested in clinical trials (402, 403); (iii) there is no licensed vaccine for RSV, but a number of promising vaccine candidates (e.g., live-attenuated RSV vaccine MEDI-559) are currently being evaluated in advanced clinical trials (404, 405); and (iv) most HCMV vaccines are produced by either attenuating HCMV to generate modified-virus vaccines or isolating subunit viral antigens to generate individual-antigen vaccines (406). Clinical trials are currently being undertaken to evaluate promising candidates (e.g., AD169, Towne/Toledo chimeric vaccines, and DNA vaccines of gB and pp65) (406, 407). The devel-

opment of HCMV vaccination still faces many challenges, such as the clinical selection of appropriate trial endpoints and the identification of viral antigens with desirable features for vaccine design (408).

Viruses Targeted by Vaccines but Not by Antiviral Drugs

As of April 2016, approved vaccines are available for 13 infectious diseases, but their antiviral drugs are still lacking. The list of approved vaccines could be summarized as follows: (i) human adenovirus vaccine (Adenovirus Type 4 and Type 7 Vaccine, Live, Oral), (ii) rotavirus vaccines (Rotarix for rotavirus serotype G1, G3, G4, or G9 and RotaTeq for rotavirus serotype G1, G2, G3, or G4), (iii) hepatitis A virus vaccines (Havrix and Vaqta), (iv) poliovirus vaccines (Kinrix, Quadracel, and Ipol), (v) yellow fever virus vaccine (YF-Vax), (vi) Japanese encephalitis virus vaccines (Ixiaro and JE-Vax), (vii) measles vaccines (M-M-R II and ProQuad), (viii) mumps vaccines (M-M-R II and ProQuad), (ix) rubella vaccines (M-M-R II and ProQuad), (x) varicella vaccine (ProQuad), (xi) rabies vaccines (Imovax and RabAvert), (xii) variola virus (smallpox) vaccine (ACAM2000), and (xiii) hepatitis E virus (HEV) vaccine (HEV239). HEV239 is the only HEV vaccine that was approved in China in 2012 (409), while many vaccine candidates are currently under examination in clinical trials (410).

In addition to the approved vaccines mentioned above, many antiviral agents have been designed. As an approved drug against HCMV, cidofovir can efficiently inhibit viral infections with human adenovirus, but clinical evidence is still lacking (411). Although no antiviral compound is formally approved for HEV, preliminary clinical observations suggest that pegylated interferon and ribavirin alone might offer a sustained virological response, but HEV clinical trials are still required (412). A number of promising compounds (e.g., hydantoin, guanidine hydrochloride, L-buthionine sulfoximine, and Py-11) can inhibit viral replication of picornavirus *in vitro*, but *in vivo* evidence from clinical trials is largely lacking (413). As for rabies infections, they are generally treatable by using postexposure prophylaxis with the administration of rabies immunoglobulin and vaccine (414). Postexposure prophylaxis must be initiated soon after rabies exposures, mostly through animal bites (415). For viral infections like polio, yellow fever, and measles, adequate protection can be achieved by vaccination in some circumstances, but the coverage of antiviral drugs is currently not available.

Off-label drugs might be considered valuable options when licensed treatments are not available. For instance, cidofovir might be an off-label prescription to treat various DNA virus infections such as human polyomavirus, adenovirus, and smallpox (416). Three drugs (foscarnet, ganciclovir, and cidofovir) approved for HCMV can also inhibit the viral DNA polymerase of human herpesvirus 6 (HHV-6) (127). Despite this, the effectiveness of off-label drugs is yet to be fully proven in clinical trials.

Viruses Targeted by neither Vaccines nor Antiviral Drugs

Apart from 22 well-known viruses targeted by vaccines and/or antiviral drugs, a great number of emerging infectious diseases without any licensed treatments are currently afflicting millions of patients (417). Therefore, a great deal of attention has been paid to many emerging viruses, such as Epstein-Barr virus (EBV) (418), human parvovirus B19 (419, 420), human norovirus (421), human rhinovirus (422), human herpesvirus 6 (127), human coronavirus (423), human astrovirus (424), human sapovirus (425), chikungunya virus (324), dengue virus (426), West Nile virus (427), Hendra virus (328), Nipah virus (328), Ebola virus (428, 429), Marburg virus (MARV) (429), Lassa virus (430), Junin virus (430), Machupo virus (431), and, most recently, Zika virus (432). Here, we briefly discuss antiviral strategies against these emerging infectious diseases.

dsDNA viruses: EBV, human polyomavirus, and herpesvirus 6. EBV, also called human herpesvirus 4, was first reported in 1964. Many antiviral drugs (e.g., valacyclovir, ganciclovir, and valganciclovir) can actively inhibit EBV replication *in vitro* or in small clinical trials, but large-scale clinical trials are still required (418, 433). EBV vaccines have been generated based on the EBV envelope glycoprotein GP350 and $CD8^+$ T cell peptide epitopes, but their effectiveness requires further improvement (418).

Human polyomavirus was first discovered by Ludwik Gross in 1953 (434). The best-known types of human polyomaviruses are JC and BK viruses, which infect >80% of adult populations (435). Recognized as promising drug candidates, human monoclonal antibodies target viral protein 1 of JC virus to inhibit JC virus infections, and they exert cross-reactivity against many JC virus strains (436). Cidofovir might be an off-label drug to treat various DNA virus infections (e.g., human polyomavirus) (416).

Human herpesvirus 6 was first isolated in patients with lymphoproliferative disorders in 1986 (437). There is no vaccine or drug licensed for human herpesvirus 6, but one experimental compound {(*R*)-9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine (H2G)} and four drugs (ganciclovir, foscarnet, cidofovir, and artesunate) approved for other clinical uses are under investigation (127).

ssDNA virus: human parvovirus B19. Human parvovirus B19, discovered in 1975, is the best-known virus in the group of ssDNA viruses. Most infections by human parvovirus B19 in immunocompetent patients do not require any treatment, because the symptoms are transient (420). Although controlled studies are still required, intravenous immunoglobulin (IVIG) therapy has been recognized as a popular alternative because it offers a good source of neutralizing antibodies in immunocompromised patients exposed to human parvovirus B19 (419). Intravenous immunoglobulin therapy substantially increases reticulocyte counts and hemoglobin levels, but 33.9% of treated patients may have a relapse at a mean of 4.3 months (438). Apart from neutralizing antibodies, a recent study suggests that cidofovir at 500 μM could significantly reduce virus infectivity *in vitro*, but clinical evidence is still required (439).

Positive-sense ssRNA viruses: Zika virus, norovirus, coronavirus, rhinovirus, astrovirus, sapovirus, dengue virus, chikungunya virus, and West Nile virus. Zika virus, discovered in 1947, was first isolated in a monkey in the Zika forest of Uganda (440). Since the first outbreak of Zika virus in the Yap Islands in 2007, Zika virus transmissions have been reported in 64 countries according to a WHO report on 13 April 2016 (http://www.who.int/). Recent evidence suggests that ~0.95% of Zika virus infections in pregnant women may lead to microcephaly (abnormally small head) in infants (441). Zika virus infections are also associated with severe neurological complications such as Guillain-Barré syndrome (440). Unfortunately, a vaccine, antiviral compound, or good serological test is not available for Zika virus today (442). Vaccine candidates are now under development, but a safe and effective vaccine will probably take 3 to 10 years (443, 444). Currently, the best prevention, especially for pregnant women

and infants, is to avoid mosquito exposure because Zika virus is transmitted mainly by infected mosquitoes.

Human norovirus was first identified in stored human stool samples in 1972. Virus-like particles containing norovirus genotype GI.1/GII.4 have been designed as vaccine candidates, and their effectiveness seems promising in phase 1 clinical trials (421). Many antiviral agents (e.g., EV71, ribavirin, and favipiravir) efficiently inhibit norovirus protease or RNA polymerase, but their development is still at an early stage (325, 326).

Human coronavirus, discovered in the 1960s, is known to cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (423). Many antiviral candidates (e.g., corticosteroids) potentially inhibit human coronavirus, and more details have been elucidated in recent review articles (445–447).

Human rhinovirus, first discovered in the 1950s, is the most common cause of upper respiratory tract infections (422). There is no vaccine or drug licensed for human rhinovirus, but a number of antiviral agents (e.g., pleconaril, vapendavir, and pirodavir) have been under investigation (422). However, it remains a challenge to develop rhinovirus drugs and vaccines, because the rhinovirus genome, classified into >100 serotypes, is highly variable (422).

Dengue, chikungunya, and West Nile viruses from the family *Flaviviridae* are mosquito-borne viruses that pose significant risks to human health throughout the world (448, 449). Dengue virus, discovered in the 1960s, is the cause of several pandemics (426). Many experimental inhibitors (e.g., sinefungin, SDM25N, and CCG-3394) have been designed to target the NS4B and NS5 proteins of dengue virus (450, 451). Although a number of vaccine candidates (e.g., CYD-TDV and TDEN) have reached advanced clinical trials (452, 453), it remains a challenge to develop dengue virus vaccines with optimal efficacy against all 4 dengue virus serotypes. As for the treatment of chikungunya virus, many antiviral drugs (ribavirin and pegylated interferon alfa) and experimental agents (e.g., chloroquine, arbidol, and chlorpromazine) may interfere with different stages of the virus life cycle (324), but clinical evidence is largely lacking. Regarding the treatment of West Nile virus, veterinary vaccines have been licensed for use in horses and dogs (454, 455). Nevertheless, vaccine candidates (454, 455) and small-molecule inhibitors (456, 457) against human West Nile virus are still under investigation.

Human astrovirus (424) and sapovirus (425) were first discovered in human diarrheic stool samples in 1975 and 1976, respectively. Astrovirus and sapovirus infections cause acute gastroenteritis in humans and animals (424, 425). Due to the lack of commercial interest, the development of vaccines and antiviral agents against human astrovirus and sapovirus is rather slow. However, improved sanitation and hygiene can efficiently prevent viral infections, because astrovirus and sapovirus are transmitted primarily through the fecal-oral route (424, 425).

Negative-sense ssRNA viruses: Ebola, Marburg, Hendra, Nipah, Lassa, Junin, and Machupo viruses. Ebola and Marburg viruses from the family *Filoviridae* were first discovered in 1976 and 1967, respectively. Both zoonotic viruses were originally transmitted from bats to humans (458). As of April 2016, there is no vaccine or antiviral drug licensed for EBOV and MARV. Phase 1/2 clinical trials have been undertaken to prove the effectiveness of treatment candidates such as favipiravir, EBOV glycoprotein vaccine (EBOVGP), and ZMapp (334, 428, 459). Moreover, convalescent-phase plasma transfusions from disease survivors might offer a valuable anti-EBOV option in resource-limited settings (459). Therapeutic strategies using chemical agents (e.g., neplanocin A, BCX4430, and lectins) against Ebola virus infections have been reviewed elsewhere (337, 460). As for the treatment of MARV infections, no drug or vaccine has been licensed, but supportive therapies are regularly applied in clinical practice (327). A recent study suggests that AVI-7288, which is a phosphorodiamidate morpholino oligomer, potentially acts as postexposure prophylaxis for MARV infections in humans (461). The efficacy of antiviral candidates (e.g., ribavirin, PMO-Plus, and monoclonal antibodies) against MARV has yet to be fully proven in clinical trials (327).

Hendra and Nipah viruses from the family *Paramyxoviridae* were first identified in 1994 and 1999, respectively. In Australia, Equivac HeV has been approved as a Hendra virus vaccine in horses (328). However, human vaccine development is hindered by limited commercial benefits, because only 7 human Hendra virus infections have been reported since 1994 (462). As for Nipah virus infections, vaccine candidates (e.g., Hendra virus soluble G glycoprotein subunit vaccine [HeV-sG]) are currently being investigated at a preclinical stage (463). Based on *in vitro* experiments, ribavirin can efficiently inhibit henipavirus replication (328). Moreover, preliminary clinical observations suggest that ribavirin may inhibit human Hendra and Nipah virus infections, despite controversial results being reported in different studies (328). Although more clinical evidence is still needed, ribavirin might be used as an off-label treatment for henipavirus infections in the absence of other therapies (328).

Junin, Lassa, and Machupo viruses are human arenaviruses from the family *Arenaviridae*. It has been shown that favipiravir can efficiently inhibit viral replication of arenaviruses (Junin, Machupo, and Pichinde viruses) (338, 339). For vaccine development, human HLA class I-restricted epitopes have been explored for human arenaviruses (430). A number of Lassa and Junin virus vaccine candidates (e.g., Candid#1, ML-29, and Tacaribe virus [TACV] vaccine) have been tested in human or animal trials (430). However, vaccine development for Lassa virus and filoviruses is hindered by a lack of commercial interest (464).

Overall, for the control of infectious diseases, both vaccination and antiviral drugs could be envisaged, but the availability of antiviral treatments varies from one virus to another. As of April 2016, 22 infectious diseases are currently treated by licensed vaccines and/or antiviral drugs, but a broad spectrum of emerging viruses is still at large. It is known that viruses from the same family usually share similar features (465), and many emerging viruses come from such virus families that possess at least one virus targeted by vaccines and/or antiviral drugs. Therefore, FDA-approved treatments might be active against emerging infectious diseases in some circumstances.

CONCLUSIONS AND FUTURE PERSPECTIVES

To our knowledge, this article presents for the first time a comprehensive overview of 90 antiviral drugs approved over the past 50 years (Fig. 1). These antiviral drugs approved for the treatment of 9 human infectious diseases have saved tens of millions of human beings over 5 decades, and they will continue to be essential for antiviral treatments against current and emerging viral infections (Fig. 2). As of April 2016, various antiviral drugs offer promising activities against HCV infections, but a definitive cure for

TABLE 4 Control of viral infections using approved vaccines and/or antiviral drugs

Group	Family	Virus(es)	Vaccine	Antiviral drug
I (dsDNA)	*Adenoviridae*	Human adenovirus	Yes	Off-label drug[a]
	Hepadnaviridae	HBV	Yes	Yes
	Herpesviridae	VZV (shingles)	Yes	Yes
		HSV, HCMV	No	Yes
		EBV	No	No
		Human herpesvirus 6	No	Off-label drug[a]
	Papillomaviridae	HPV	Yes	Yes[b]
	Polyomaviridae	Human polyomavirus	No	Off-label drug[a]
	Poxviridae	Variola virus (smallpox)	Yes	Off-label drug[a]
II (ssDNA)	*Parvoviridae*	Human parvovirus	No	No
III (dsRNA)	*Reoviridae*	Rotavirus	Yes	No
IV [(+)ssRNA]	*Astroviridae*	Human astrovirus	No	No
	Caliciviridae	Human sapovirus	No	No
	Coronaviridae	Human coronavirus	No	No
	Flaviviridae	HCV	No	Yes
		Yellow fever virus	Yes	No
		Japanese encephalitis virus	Yes	No
		Dengue, West Nile, Zika viruses	No	No
	Hepeviridae	Hepatitis E virus	Yes[c]	No
	Picornaviridae	Hepatitis A virus, poliovirus	Yes	No
		Norovirus, rhinovirus	No	No
	Togaviridae	Rubella virus	Yes	No
		Chikungunya virus	No	No
V [(−)ssRNA]	*Arenaviridae*	Lassa, Junin, Machupo viruses	No	No
	Filoviridae	Ebola, Marburg viruses	No	No
	Orthomyxoviridae	Influenza virus	Yes	Yes
	Paramyxoviridae	RSV	No	Yes
		Measles, mumps	Yes	No
		Hendra, Nipah viruses	No	Off-label drug[a]
	Rhabdoviridae	Rabies	Yes	No
VI [(+)ssRNA]	*Retroviridae*	HIV	No	Yes

[a] Cidofovir might be an off-label prescription to treat human polyomavirus, adenovirus, and smallpox. Foscarnet, ganciclovir, and cidofovir might be off-label drugs for HHV-6. Ribavirin might be an off-label prescription for Hendra and Nipah virus infections.
[b] Three FDA-approved drugs (sinecatechins, podofilox, and imiquimod) are available for the treatment of external genital warts caused by HPV (354). However, these drugs may not target HPV proteins directly.
[c] The HEV vaccine HEV239 was approved in China in 2012.

HIV, HBV, HCMV, HPV, HSV, RSV, VZV, or influenza virus is yet to be discovered. In addition to approved antiviral drugs, our review also highlights several forthcoming antiviral regimens in phase 3 clinical trials (Table 3), because promising inhibitors (e.g., marine natural products [394]) have continuously been developed to fight against current and emerging infectious diseases.

During the past 5 decades, great achievements have been made in the field of antiviral drug discovery. As of April 2016, many antiviral drugs and/or vaccines have been approved for the treatment of 22 infectious diseases: HIV, HBV, HCV, HCMV, HPV, HSV, RSV, VZV, influenza virus, smallpox, rotavirus, human adenovirus, human herpesvirus 6, poliovirus, hepatitis A virus, hepatitis E virus, Japanese encephalitis virus, yellow fever, rubella, measles, mumps, and rabies (Table 4). Nevertheless, there is still no antiviral drug or vaccine for more than 200 infectious diseases that are afflicting human populations worldwide. In order to highlight the latest progress in antiviral drug discovery, our review provides a brief summary of potential antiviral agents and vaccines against 41 infectious diseases. It is our belief that new antiviral treatments will be formally approved to cure a broad range of emerging infectious diseases in the future.

Importantly, antiviral compounds with broad-spectrum activity against different virus genotypes or subtypes are still welcome, because the effectiveness of most antiviral drugs is limited to only certain viral strains (466). For instance, some antiviral drugs (e.g., amprenavir) inhibit only HIV-1 but not HIV-2 (173). Many HCV inhibitors have been approved only for HCV genotype 1 but not for other genotypes (Table 2). Nevertheless, a number of antiviral inhibitors (brivudine, acyclovir, TDF, foscarnet, famciclovir, lamivudine, ribavirin, valacyclovir, PegIFNα-2a, and PegIFNα-2b) have been licensed for the treatment of more than one virus (Table 2), supporting the idea of developing antiviral drugs against multiple infectious diseases in the future.

Despite the rapid advancement of pharmaceutical and biotechnological approaches (e.g., RNA interference [RNAi] [467]), the development of successful antiviral treatments remains a challenge. First, potent antiviral drugs that counteract the highly variable nature of virus genomes are still required, because emerging

drug resistance mutations remain a major cause of treatment failure (10, 466, 468, 469). Second, it is difficult to eradicate viral reservoirs using antiviral agents, because DNA viruses and retroviruses can integrate their genomes into human genomes (470, 471). Third, it remains a challenge to rapidly develop antiviral drugs and vaccines against emerging infectious diseases, calling for a joint effort between scientific and industrial partners. Fourth, it is a challenge to pursue effective, low-toxicity, and well-tolerated drugs that enhance patient compliance and drug administration (472). Fifth, efficient antiviral treatments against viral coinfections (e.g., HIV/HBV coinfections [473]) require further investigations. Sixth, access to and delivery of costly new therapies are becoming increasingly problematic in resource-limited settings (474). Political and financial commitment is also vital to eliminate substandard and counterfeit antiviral drugs that threaten global public health (475).

Encouraged by the accelerated pace of drug discovery in the past 5 decades, we anticipate that novel antiviral therapeutics will ultimately contribute to elimination and eradication strategies against human infectious diseases in the future.

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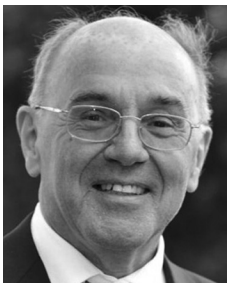

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